This supplement contains the following items:

1. The original protocol (in place when the first patient was recruited), the final protocol, a summary of all changes between these protocol versions.

2. The statistical analysis plan (there was no changes made to the statistical analysis plan)

CLINICAL TRIAL PROTOCOL

Proton Pump Inhibitors vs. Histamine-2 REceptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC)

A multi-centre, cluster randomised, crossover, registry trial comparing the safety and efficacy of proton pump inhibitors with histamine-2 receptor blockers for ulcer prophylaxis in intensive care patients requiring invasive mechanical intervention

Protocol Version: Version 2.0
24 November 2015

UTN: U1111-1151-5142
ANZCTRN: pending
Ethics Approval: 15/NTB/52
Funding: Health Research Council, New Zealand
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ABBREVIATIONS

ANZICS = Australian and New Zealand Intensive Care Society
CTG = Clinical Trials Group
GI = Gastrointestinal
H_2RB = Histamine-2 receptor blocker
ICU = Intensive Care Unit
M-H = Mantel Haenszel
PPI = proton pump inhibitor
SUP = stress ulcer prophylaxis

1 GENERAL INFORMATION

1.1 Title

A multi-centre, cluster randomised, crossover, registry trial comparing the safety and efficacy of proton pump inhibitors with histamine-2 receptor blockers for ulcer prophylaxis in intensive care unit patients requiring invasive mechanical ventilation.

1.2 Chief investigator

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1.4 Participating centres

Participating centres have not yet been confirmed; however, the following centres have expressed interest in participating in this study:

- Armadale Hospital
- Auckland City Hospital (Department of Critical Care Medicine)
- Auckland City Hospital (Cardiovascular Intensive Care Unit)
- Austin Hospital
- Alfred Hospital
- Bendigo Hospital
- Bunbury Hospital
- Canberra Hospital

- Christchurch Hospital
- Concord Hospital
- Freemantle Hospital
- Geelong Hospital
- Gold Coast University Hospital
- Hawkes Bay Hospital
- Liverpool
- Middlemore Hospital
- Nepean Hospital
- Nelson Hospital
- Northern Hospital
- North Shore Hospital
- Princess Alexandra Hospital
- Queen Elizabeth Hospital
- Royal Hobart Hospital
- Royal Melbourne Hospital
- Royal North Shore Hospital
- Royal Prince Alfred Hospital
- Royal Perth Hospital
- Sir Charles Gairdner
- St Vincent's Melbourne
- St Vincent's Hospital, Sydney
- St Vincent's University Hospital, Dublin (& at least six other Irish ICUs)
- Tauranga Hospital
- St George Hospital
- Wellington Hospital
- Western Hospital
- Whangarei Hospital
- Wollongong Hospital

1.5 Coordinating Centre

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2 LAY SUMMARY

2.1 Stress ulcers in the Intensive Care Unit

Patients who require treatment in the Intensive Care Unit (ICU) can develop stomach ulcers or duodenal (small intestine) ulcers. This occurs most commonly when life support (a breathing machine) is required or when the patient develops a bleeding tendency as a result of their illness. These kinds of ulcers are known as 'stress ulcers' and may cause life-threatening bleeding.

2.2 Prevention of stress ulcers in the Intensive Care Unit

Patients who require life support in the ICU are typically given one of two types of medicine to try and prevent the development of stress ulcers. The two types of medicines are called 'proton pump inhibitors' (PPIs) and 'histamine-2 receptor blockers' (H_2RBs). While the prevention of stress ulcers is very important, the medicines used to prevent ulcers may have important side effects including an increased risk of developing certain kinds of infections. The risk of side effects may depend on the medication used.

2.3 Purpose of the study

This study will establish which of the two types of medicines that are commonly used for stress ulcer prophylaxis in ICU patients who require life support leads to the lowest risk of upper gastrointestinal bleeding, prolonged mechanical ventilation, and *Clostridium difficile* infection.

2.4 Study design

The study will use a design known as a 'cluster crossover registry design'. In this type of study, data are collected primarily from existing data sources rather than the medical records of individual patients. There will be two study treatment periods. During the first treatment period, half of the participating ICUs will be randomly (like the toss of a coin) instructed to use PPIs for stress ulcer prophylaxis in patients who require life-support while the other half will use H_2RBs. During the second treatment period each ICU will swap to using the opposite treatment. This means that, in situations where PPIs and H_2RBs are regarded as being equivalent by the treating clinician, the treatment administered to the patients will be determined based on the treatment assigned to the patient's ICU. However, if there is a specific indication for either PPI treatment or H_2RB treatment (for example, an allergy), the treatment indicated for the particular patient concerned will be administered irrespective of the treatment assigned to the ICU. In other words, in this study, all patients will receive the treatment that the treating clinician believes to be in their best interests irrespective of the default treatment assigned to the ICU.

2.5 Study importance

This study will enrol >15 times as many patients as have been studied in all previous clinical trials comparing approaches to stress ulcer prophylaxis in the ICU combined[1]. The study will provide robust estimates of the relative risk

of clinically significant upper gastrointestinal (GI) bleeding and complications that are potentially related to using PPIs vs. H_2RBs for stress ulcer prophylaxis, a treatment currently given to an estimated 2.5 million ICU patients per year in developed countries alone.

In addition to the direct clinical benefit of comparing stress ulcer treatments, the study utilises an innovative design that has the potential to revolutionise the conduct of clinical trials both in the ICU and in other areas of medicine. Compared with current standard parallel group RCTs, a 'cluster crossover' trial using existing data sources to obtain data provides the opportunity to efficiently detect small, but clinically important, treatment effects rapidly and for comparatively lower cost.

3 SYNOPSIS

Overview	Multi-centre, cluster crossover, randomised trial comparing proton pump inhibitors (PPIs) with histamine-2 receptor blockers (H_2RBs) for ulcer prophylaxis in mechanically ventilated ICU patients.
Design	Cluster crossover trial using registry data.
Participants	All mechanically ventilated patients aged ≥18 years except for those whose ICU admission diagnosis is upper GI bleeding.
Intervention	Study treatment is open label PPIs vs. H_2RBs as the default routine therapy for ulcer prophylaxis. Each study ICU will use PPIs or H_2RBs as routine therapy for a period of six months. At the end of this six month period, the ICU will then swap to the opposite routine ulcer prophylaxis strategy which will then be used for the next six months. Study treatment will only be administered in situations where the treating clinician believes ulcer prophylaxis is in the patient's best interests and, irrespective of the treatment assigned to the ICU, either a PPI or an H_2RB can be used for an individual patient, if the treating clinician believes that a particular treatment is indicated.
Primary end point	Major complications arising during the ICU admission (censored at 90 days), using a composite end point comprising the following: (i) clinically significant upper GI bleeding (ii) *Clostridium difficile* infections (iii) episodes of mechanical ventilation of more than 10 days
Secondary end points	1. In hospital mortality (censored at 90 days) 2. Upper gastrointestinal bleeding The principal end point of interest in relation to upper GI bleeding is the

	cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU. Clinically significant upper GI bleed is defined as: overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or visualised by upper GI endoscopy) AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in haemoglobin of at least 20 g/L, or 4) transfusion of 2 units of packed red blood cells or more). 3. *Clostridium difficile* infections. Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients in whom a positive specimen was collected prior to ICU admission) 4. Hours of mechanical ventilation per patient 5. ICU length of stay per patient 6. Hospital length of stay per patient
Statistical considerations and sample size	Our planned sample size of approximately 25360 patients will provide 90% power to detect a 2.4% absolute difference in our composite endpoint. This sample size is based on a baseline composite endpoint rate of 12.0% with 40 participating ICUs enrolling an average of 317 patients per 6 month study period with a coefficient of variation of 0.60 in numbers of patients per cluster per period. It incorporates a within-cluster-within-period correlation of 0.030 and within-cluster-between-period correlation of 0.024, as observed in the ANZICS CORE Adult Patient Database in 2013 for duration of mechanical ventilation > 10 days, which is the most frequent component of the composite endpoint.

4 BACKGROUND AND RATIONALE

4.1 The 'cluster crossover registry trial'.

One of the factors responsible for the large number of negative trials in the field of intensive care medicine is that 'effect sizes' attributable to treatments being tested are often exaggerated[2]. One of the problems investigators face is that conducting a conventional randomised controlled trial (RCT) with a large enough sample size to detect realistic treatment effects is generally prohibitive in terms of both logistics and cost. Instead, we propose an innovative study design combining two novel trial methodologies: cluster crossover randomisation[3] and collection of outcome data from existing data sources[4]. This design offers the dual prospect of generating the statistical power necessary to evaluate candidate interventions with small effect sizes and of being much cheaper than a conventional RCT because it uses data that are already collected for other purposes.

The cluster crossover design will randomise entire ICUs rather than individual patients. Each ICU will define a cluster and each ICU will cross over to use both of the treatment approaches being tested by the end of the study. Existing registry data sources will be used to collect baseline, intervention, and outcome data for the patients admitted to the study ICUs during the trial. Recent academic discourse has highlighted the potential for 'big data' to advance medical knowledge[5] but the idea of performing a large scale randomised trial relying on multiple existing data sources is a new innovation in clinical research. In addition to being innovative, we contend that this is also the optimal trial design for testing ubiquitous ICU interventions where the necessary data are already being collected for quality assurance and other purposes, and where clinical equipoise exists for testing two accepted treatment regimens. This methodology has the potential to revolutionise the conduct of clinical trials in the ICU and in other areas of medicine. In the ICU there are many interventions that could be tested using this approach in the future.

4.2 The cluster crossover registry trial and the choice of stress ulcer prophylaxis

The type of stress ulcer prophylaxis used in the ICU is a logical choice for the initial intervention to test in a cluster crossover registry trial because:

1. Published RCTs lack adequate power to confirm or refute the existence of clinically important treatment effects suggested by observation studies[1], [6-8]
2. An adequately powered traditional parallel-group RCT would be prohibitively costly to perform
3. Existing data sources can be used to collect clinically important outcomes [9]
4. The use of PPIs or H_2RBs for stress ulcer prophylaxis is a common ICU intervention and the best agent to use is uncertain[10]
5. There is a strong biological rationale for believing that the choice of stress ulcer prophylaxis influences clinically important outcomes

4.3 Comparative effectiveness of PPIs and H_2RBs for stress ulcer prophylaxis

4.3.1 Upper GI bleeding

4.3.1.1 The importance of upper GI bleeding in the ICU

In a prospective multicentre cohort study conducted in 1994, clinically important upper gastrointestinal haemorrhage occurred in 1.5% (95% CI; 1.0-2.1%) of ICU patients. The mortality rate was 48.5 percent in the group with bleeding and 9.1 percent in the group without bleeding ($P < 0.001$)[11]. We have recently shown that, across seven tertiary ICUs in Australia and New Zealand, the median percentage per ICU of patients with new upper GI bleeding complicating ICU admission is 1.4% (IQR 0.3-1.8)[9] and a large, high quality, international observational cohort study demonstrated an incidence of 2.5%[12].

4.3.1.2 Stress ulcer prophylaxis in the ICU

The perceived importance of stress ulcer prophylaxis is highlighted by its incorporation into quality-oriented checklists for the care of the critically ill such as the FASTHUG mnemonic where the letter 'U' stands for ulcer prophylaxis[13]. There is uncertainty about which type of ulcer prophylaxis is preferred. The Surviving Sepsis Campaign guidelines recommend the use of PPIs[14] while the Society of Critical Care Medicine recommend H_2RBs[15]. In a recently conducted survey, ICU specialists from Australia and New Zealand estimated that, in their ICUs, an average of 84% of ventilated patients receive stress ulcer prophylaxis[10]. This is in agreement with a recently, conducted survey of ICU specialists from Ireland, of whom 85% give ventilated patients stress ulcer prophylaxis, 80-100% of the time (personal communication-AN). As is the case in other parts of the world[16, 17] PPIs and H_2RBs are the most common medicines given for stress ulcer prophylaxis in Australia[9, 10]. Irish Intensivists use PPI 83% of the time and H_2RBs 13% of the time (n=91) when administering SUP personal communication-AN).

4.3.1.3 The risk of upper GI bleeding with PPIs vs. H_2RBs

Overall, PPIs may be more effective at reducing upper GI bleeding than H_2RBs[1]. In a recent systematic review and meta-analysis comparing PPIs with H_2RBs for ulcer prophylaxis in the ICU, fourteen trials enrolling 1,720 patients reported an end point of overt upper gastrointestinal bleeding. The use of PPI resulted in a significantly lower risk of overt bleeding than the use of H_2RB (RR 0.35; 95% CI 0.21-0.59; $P<0.0001$; $I^2 = 15\%$) (see Figure 2)[1]. Although these data constitute level I evidence that PPIs are more effective at reducing upper GI bleeding than H_2RBs, possible publication bias and weaknesses in trial methodology mean that there remains uncertainty about this apparent difference[1]. Paradoxically, recent data suggest that PPIs might actually be associated with an increased risk of clinically significant bleeding in the ICU population compared to H_2RBs[9, 15].

Figure 1 Forest plot for overt upper gastrointestinal bleeding for stress ulcer prophylaxis vs. placebo. Data from 14 trials were included in the analysis using random effects model. M-H: Mantel Haenszel; SUP: Stress Ulcer Prophylaxis. Reproduced from Krag et al[18]

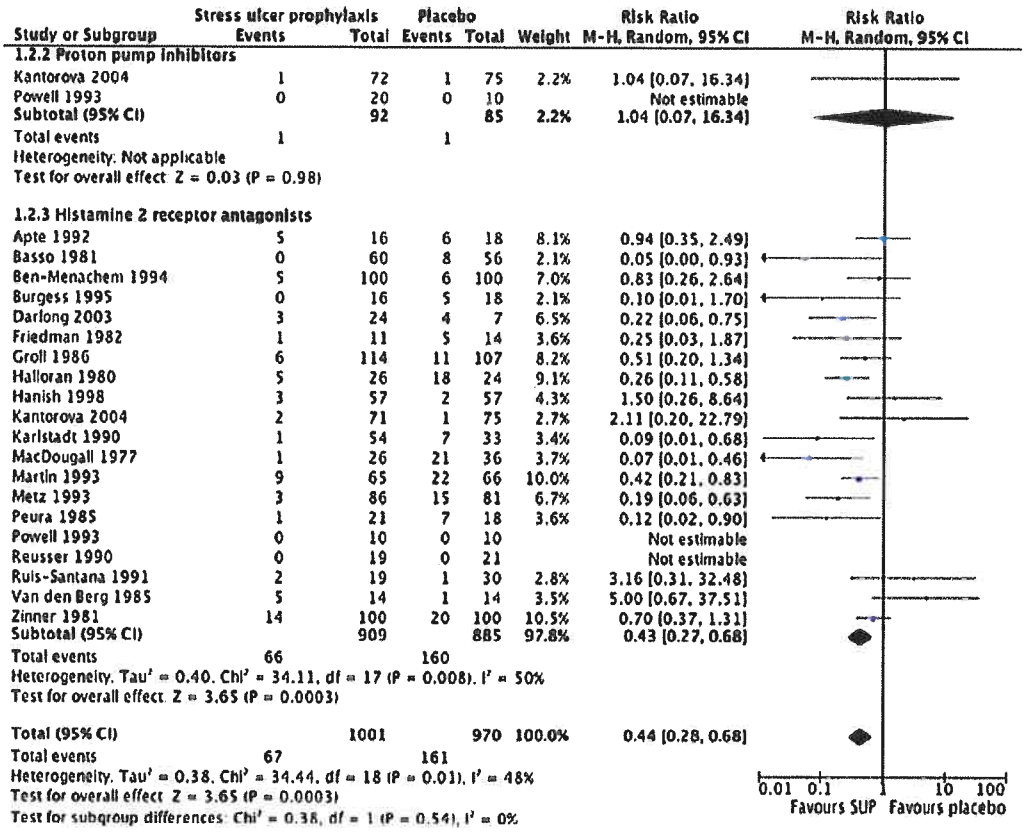
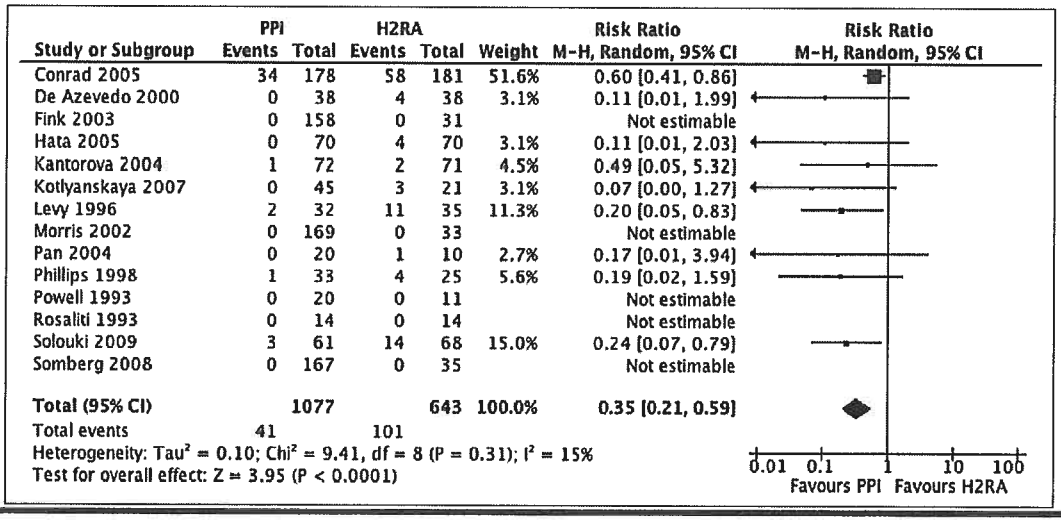


Figure 2 Forest plot for overt upper gastrointestinal bleeding outcome. Data from 14 trials were included in the analysis using random effects model. M-H Mantel Haenszel. reproduced from Alhazzani et al[1]



4.3.2 Hospital acquired pneumonia

4.3.2.1 The importance of hospital acquired pneumonia in the ICU

Hospital acquired infections including pneumonia are associated with prolonged hospital stays, increased health care resource utilisation, and increased mortality risk[19].

4.3.2.2 The biological basis by which choice of ulcer prophylaxis may influence pneumonia risk

The aspiration of gastric bacteria is a frequent source of airway colonisation and appears to have a pathophysiological role in the development of pneumonia in ICU patients. In ventilated ICU patients, the number of Gram negative bacilli in gastric aspirates increases as the gastric pH increases[20]. PPIs cause more profound acid suppression[21] and lead to significantly more bacterial overgrowth of the stomach and duodenum than H_2RBs[22].

In addition to promoting bacterial overgrowth, PPIs appear to exert a range of immunosuppressive effects[23]. For example, lansoprazole induces significant inhibition of human natural killer cell activity, reduces polymorphonuclear cell chemotaxis, and decreases superoxide generation[24]. Omeprazole also inhibits natural killer cells suggesting that that the suppression of natural killer cell function is a class effect of PPIs[25]. Similarly, in healthy volunteers, a single 40mg dose of omeprazole leads to a reduction in neutrophil reactive oxygen production and reduces neutrophil bactericidal capacity by 30%[26]. While the clinical significance of the immunosuppressive effects of PPIs is uncertain, these data lend weight to the hypothesis that using PPIs for ulcer prophylaxis rather than H_2RBs might increase pneumonia risk.

4.3.2.3 Observational studies comparing the pneumonia risk of patients treated with PPIs vs. H_2RBs

In the community setting, use of acid-suppressive medicines appears to be a risk factor for the subsequent development of pneumonia[27]. PPIs are associated with a greater pneumonia risk than H_2RBs and a significant positive dose-response relationship for pneumonia risk is present among PPI users[27]. Emphasising the potential differential risk associated with the choice of medication for ulcer prophylaxis, a case-control series comparing 7297 patients with pneumonia with 9993 matched controls, showed that the relative risk of newly diagnosed community-acquired pneumonia was increased with current use of PPIs (RR = 1.16 [95% confidence interval 1.03-1.31]) but not with the use of H_2RBs (0.98 [0.80-1.20])[28]. Similarly, in a cohort study including 63,878 hospital admissions (but excluding patients requiring ICU admission) the incidence of hospital-acquired pneumonia was higher in the patients exposed to acid-suppressive medication than in the unexposed group (4.9% vs 2.0%; odds ratio [OR], 2.6; 95% confidence interval [CI], 2.3-2.8). In this study, after multivariate logistic regression, the association between acid suppressive medications and pneumonia risk was significant for PPIs (OR, 1.3; 95% CI, 1.1-1.4) but not for H_2RBs (OR, 1.2; 95% CI, 0.98-1.4)[7].

In the ICU setting, PPI use is associated with increased pneumonia risk compared to H_2RB use. In a 35,312-patient retrospective cohort study of

adults requiring mechanical ventilation for 24 hours or more and administered either an H_2RB or PPI for 48 hours or more while intubated, pneumonia occurred in 38.6% of PPI-treated patients vs. 27% of H_2RB-treated patients (P<0.001)[8]. Using propensity score adjusted multivariate regression modelling to control for confounders, PPI use was associated with a significantly increased risk of pneumonia compared to H_2RB use (OR 1.2; 95% CI 1.03-1.41)[8]. Similarly, in a single centre retrospective study of cardiothoracic surgical patients, treatment with a PPI was found to be associated with a markedly elevated risk of nosocomial pneumonia (OR 6.6; 95% CI 2.9 to 14.9)[29]. After propensity adjusted, multivariable logistic regression, PPI treatment was found to be an independent risk factor for nosocomial pneumonia (adjusted OR 2.7, 95% CI 1.1-6.7) compared to H_2RB treatment[29]. These findings were subsequently replicated in a larger multicentre retrospective cohort study published recently in the *BMJ* (see Table 1)[6].

Table 1 Relative risk of postoperative pneumonia in patients undergoing coronary artery bypass graft surgery treated with PPI compared with H_2RB (reproduced from Bateman et al[6])

Analysis	No of outcomes/No of patients		Risk ratio (95% CI)	Risk difference (95% CI) per 1000 patients
	PPI	H2RA		
Unadjusted	492/9830	487/11 384	1.17 (1.04 to 1.32)	7.3 (1.6 to 13.0)
Age, sex, race, calendar year adjusted	492/9830	487/11 384	1.19 (1.04 to 1.36)	—
Propensity score tenths stratified	411/8514	421/10 059	1.19 (1.03 to 1.38)	—
Propensity score matched	369/7537	323/7537	1.14 (0.99 to 1.32)	6.1 (−0.6 to 12.8)

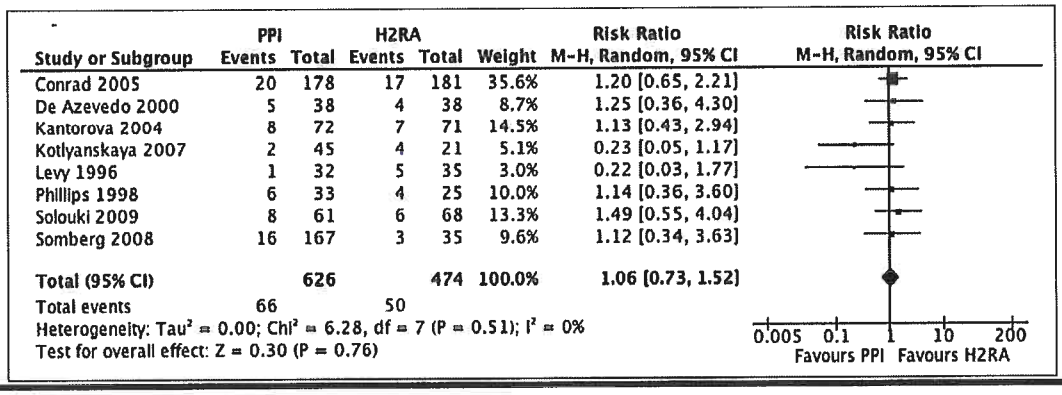
In this study, patients undergoing coronary artery bypass graft surgery who received prophylaxis with PPIs had an increased risk of postoperative pneumonia compared to patients treated with H_2RBs (OR 1.17; 95% CI 1.04 to 1.32)[6]. This risk remained after adjustment for confounding factors using multiple analytic approaches.

Overall, observational data support the hypothesis that using a PPI instead of an H_2RB for stress ulcer prophylaxis in the ICU predisposes patients to developing hospital-acquired pneumonia.

4.3.2.4 Randomised controlled trials comparing the pneumonia risk of patients treated with PPIs vs. H_2RBs

A recent meta-analysis of randomised controlled trials comparing PPIs with H_2RBs in critically ill patients identified only eight trials, enrolling a total of 1,100 patients, reporting the acquisition of nosocomial pneumonia as an outcome variable (see Figure 3)[1].

Figure 3 Forrest plot for nosocomial pneumonia risk in ICU patients receiving PPI vs H_2RB for ulcer prophylaxis (RR 1.06; 95% CI 0.73-1.52); M-H: Mantel Haenszel; PPI proton pump inhibitor) reproduced from Alhazzani et al[1].



Even when combined in a meta-analysis, the available sample is inadequate to provide the statistical power necessary to detect the small but potentially very important increase in pneumonia risk with PPI use suggested by the observational data. Indeed, estimates of precision for the relative risk of pneumonia with PPIs vs. H_2RBs do not exclude the possibility that PPI use increases the risk of hospital-acquired pneumonia by 50% compared to using H_2RBs. The most appropriate conclusion to draw from the current randomised controlled trial data is that studies with adequate power have not been performed. Recent data highlight that any differential effect of PPIs vs. H_2RBs on pneumonia risk is likely to be the greatest determinant of the relative cost-effectiveness of these medicines[30].

4.3.2.5 Summary

There is a substantial body of literature supporting the hypothesis that the choice of medication administered for ulcer prophylaxis affects the risk of developing pneumonia in ICU patients. Observational trials suggest that use of PPIs may increase the risk of developing pneumonia by 20% compared to H_2RBs. The existing evidence-base from randomised controlled trials is insufficient to exclude an effect of this magnitude.

4.3.3 Clostridium difficile infection

No randomised trials of PPIs vs. H_2RBs have reported *Clostridium difficile* colitis as an outcome measure. However, a systematic review of 12 observational studies evaluating 2,948 patients found that the development of *Clostridium difficile* infection was associated with the use of PPIs and H_2RBs[31]. The association for PPI use was greater (OR 2.05; 95% CI 1.47-2.85) than for H_2RB use (OR 1.47; 95% CI 1.06-2.05) although, the difference in the strength of the association was not significant[31]. A recent prospective *NEJM* study designed to identify host and pathogen risk factors for *Clostridium difficile* infection and colonisation showed that PPI-use was associated with an increased risk of health-care associated *Clostridium difficile* infection (OR 2.64; 95% CI 1.71-4.09) but that H_2RB use was not (OR 0.98; 95% CI 0.55-4.09)[32]. In a recent cohort study evaluating 35,312 adult patients from 71 hospitals requiring mechanical ventilation for ≥24 hours and administered an H_2RB or PPI for ≥48 hours while intubated, use of PPIs

instead of H_2RBs was independently associated with an increased risk of *Clostridium difficile* infection (OR 1.29; 95%CI 1.04-1.64)[8]. Overall, any differential effect of PPIs and H_2RBs on the incidence of *Clostridium difficile* colitis is uncertain. However, it is biologically plausible that the type of ulcer prophylaxis alters the risk of developing this important complication.

4.4 Summary of the background

PPIs and H_2RBs are both used commonly for stress ulcer prophylaxis in Australia, New Zealand, Ireland, and in other parts of the world. However, the relatively small number of subjects who have been studied in randomised trials limits the existing trial data comparing PPIs and H_2RBs for ulcer prophylaxis in the ICU. It appears that the choice between a PPI and a H_2RB for ulcer prophylaxis may alter a patient's risk of developing upper GI bleeding, pneumonia, and *Clostridium difficile* infection. Clinical trials of adequate size to determine the magnitude of any risk differences have not been performed and are a high priority given the widespread use of these medicines.

5 OBJECTIVES

The overall objective of this study is ***to establish the number of complications which occur using PPIs vs. H_2RBs for routine ulcer prophylaxis in mechanically ventilated patients in the ICU using a composite end point consisting of: (i) clinically significant upper gastrointestinal bleeding, (ii) prolonged mechanical ventilation, and, (iii) Clostridium difficile infection.***

In addition, the study will establish the relative efficacy and safety of using PPIs vs. H_2RBs in the mechanically ventilated patients in ICU with respect to:

1. The risk of in-hospital mortality (censored at 90 days)
2. The risk of developing clinically significant upper gastrointestinal bleeding.
3. The risk of developing an infection with *Clostridium difficile* while in ICU.
4. Duration of mechanical ventilation.
5. ICU and hospital length of stay.

6 STUDY DESIGN

6.1 General

This study is a randomised, multicentre, multinational, cluster cross over registry trial designed to establish the safety and efficacy of using PPIs vs. H_2RBs as the routine strategy for ulcer prophylaxis in mechanically ventilated ICU patients. The study will be divided into two treatment periods of six months. During the first treatment period, half of the ICUs will use PPIs for routine ulcer prophylaxis while the other half of the ICUs will use H_2RBs. During the second treatment period, each ICU will use the opposite treatment strategy. The treatment order will be randomised.

6.2 Study centre eligibility criteria

6.2.1 Inclusion criteria

1. Any non-paediatric ICU that routinely manages mechanically ventilated patients will potentially be eligible to participate in the study.

6.2.2 Exclusion criteria

1. ICUs that are unable or unwilling to follow the trial protocol, or
2. ICUs that are unable to capture the required study data

6.3 Individual patient eligibility criteria

6.3.1 Inclusion criteria

1. Patients aged 18 years or older who are invasively mechanically ventilated at any time during an ICU admission.

6.3.2 Exclusion criteria

1. Patients who are admitted to ICU with upper GI bleeding (APACHE III admission diagnostic codes 303, 305, and 1403)

6.4 Baseline data

The following baseline data will be collected from the ANZICS-CORE Adult Patient Database:

- Age
- Gender
- Admission type (elective vs. emergency)
- ICU admission source (i.e. ED vs. ward vs. theatre vs. other hospital)
- Chronic APACHE co-morbidities
- APACHE-III admission diagnosis[33]
- Illness severity based on the on the APACHE-II and III scores and risk of death, and "ANZ Risk of Death" models score[33]

6.5 Study treatments

This study is designed to compare two *approaches* to ulcer prophylaxis in the ICU. It will compare the open label use of PPIs with the use of H_2RBs as the default therapy for ulcer prophylaxis. The treating clinician will be able to use either a PPI or an H_2RB in rare situations where a particular treatment is clearly preferable. Patients who are usually taking a PPI or an H_2RB will switch to the treatment strategy assigned to the ICU for the duration of their ICU stay unless the treating clinician believes that this is inappropriate for the particular patient being treated. If overt upper gastrointestinal bleeding occurs, then a PPI will be administered in accordance with standard clinical practice, irrespective of treatment allocation.

While study treatment (PPI or H_2RB) will be administered for ulcer prophylaxis at the discretion of the treating clinician, routine administration of study treatment to patients receiving mechanical ventilation is expected to occur in line with current standard care[10]. The duration of study treatment will be until death, ICU discharge, or until the treating clinician no longer believes

ulcer prophylaxis is indicated. The total amount of PPI and H_2RB dispensed in each of the study ICUs will be collected for each of the study periods. Once a month, at a set time, each participating ICU will record the number of ventilated patients in the ICU receiving a PPI, the number of ventilated patients receiving an H_2RB, and the number of ventilated patients who are not receiving any stress ulcer prophylaxis. At the same time point, we will also collect the same data limited to the patients who are ventilated and on their second day in ICU (i.e. the day after ICU admission). In participating ICUs with electronic prescribing records the proportion of study patients in each treatment period who receive PPI or H_2RB and the total average dose will be recorded.

6.6 Treatment allocation

At the beginning of the study, half of the study ICUs will be randomly assigned to using H_2RBs for routine ulcer prophylaxis while the other half will be assigned routinely using PPIs. During the second treatment period ICUs will crossover to the opposite treatment. The order in which ICUs use the treatments will be determined by an independent statistician using a computer algorithm.

6.7 Outcome measures

Censoring of all study end points will apply at the time of hospital discharge following the index ICU admission or at 90 days (whichever is earlier).

6.7.1 Primary outcome measure

The primary outcome measure is a composite end point comprising the cumulative incidence of the following complications:

- Clinically significant upper GI bleeding
- *Clostridium difficile* infections
- Episodes of mechanical ventilation of more than 10 days.

6.7.2 Secondary outcome measures

6.7.2.1 In-hospital all cause mortality (Censored at day 90).

6.7.2.2 Upper gastrointestinal bleeding

The principal end point of interest in relation to upper GI bleeding is the cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU.

Clinically significant upper GI bleed is defined as:
overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or upper GI endoscopy)
AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in hemoglobin of at least 20 g/L or 4) transfusion of 2 units of packed red blood cells or more).

6.7.2.3 *Clostridium difficile* infection rates
The specific end point which will be reported in relation to *Clostridium difficile* infection rates is the:

- Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients who had positive tests from specimens collected prior to ICU admission)

6.7.2.4 Hours of mechanical ventilation

6.7.2.5 ICU length of stay

6.7.2.6 Hospital length of stay

7 FEASIBILITY

The ICUs in Australia, New Zealand and Ireland involved in the study have an established research infrastructure and have participated in a number of large scale studies leading to a number of recent NEJM publications[34-39]. We have completed a multicentre, multinational, feasibility study demonstrating that practice varies between ICUs in Australia and New Zealand[9], and Ireland (personal communication [AN]). In this study, which included seven ICUs, we were able to collect information from databases and registries on dispensing PPIs and H_2RBs, episodes of GI bleeding, *Clostridium difficile* infections, and respiratory tract colonisation with pathogenic organisms[9]. Our data confirm that collection of the outcomes relevant to an interventional trial of stress ulcer prophylaxis in the ICU using only existing data sources is feasible in a cohort of Australian, New Zealand, and Irish ICUs[9]. Furthermore, in recent surveys of ICU specialists from Australia and New Zealand and Ireland the majority of respondents (89% and 79% respectively) indicated that their belief was that there was currently insufficient evidence to determine the optimal medicine for stress ulcer prophylaxis in ICU patients and there was broad agreement that a large-scale comparative effectiveness trial is required[10].

The statistical team at the Australian and New Zealand Intensive Care Research Centre, who will conduct the statistical analyses, are familiar with the data being used in the study. The study will be co-ordinated from the MRINZ which has extensive experience in conducting similar multicentre RCTs including the 0.9% Saline vs. PlasmaLyte 148 for ICU fluid Therapy (SPLIT) trial (ACTRN12613001370796), a large-scale cluster crossover trial using individual patient data collection methods.

8 ETHICS

8.1 Guiding principles

This study is to be performed in accordance with *World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects* (WMA 2008), the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2002), the *ICH Harmonised Tripartite Guideline: Guideline for good clinical practice* (ICH 1996), the WHO *Ethical issues in Patient Safety Research: Interpreting*

existing guidance (WHO 2013), and the New Zealand Health and Disability Ethics Committee *Ethical Guidelines for Interventional Studies (the Guidelines)*.

8.2 Legal issues in this study

This trial will be conducted in compliance with relevant New Zealand (NZ) legislation including the Health Information Privacy Code, the Health and Disability Code and the NZ Bill of Rights (NZBOR) Act. This trial does not involve 'experimental' interventions. Instead, it evaluates 'standard treatments' in a systematic way in order to allow clinicians to understand how to best care for critically ill patients in the future.

8.3 Ethical issues in this study

Patterns of practice in different hospitals are often idiosyncratic and unscientific[40]. Indeed, much of clinical medicine remains empirical and local medical opinion and supply of resources are often more important than science in determining how medical care is delivered[40]. Wide variations that characterise usual clinical practice often have no basis in science but may have important implications for patient outcomes. Where there are two distinct approaches without clear evidence that one approach or the other is superior, we believe that there is an ethical imperative to conduct research to establish which approach is best.

All patients enrolled in this trial will lack capacity to give consent at the time stress ulcer prophylaxis is administered. In usual clinical practice stress ulcer prophylaxis is administered to non-consenting ICU patients as part of routine treatment because administration of stress ulcer prophylaxis is considered to be in the patient's best interest. In this study all patients with a clinical indication for stress ulcer prophylaxis will receive one of two standard treatments (PPI or H_2RB for ulcer prophylaxis). Stress ulcer prophylaxis is one of many treatments which are considered to be part of routine ICU care and is typically not specifically discussed with patients or their relatives. We do not consider that it would be ethically appropriate to withhold stress ulcer prophylaxis from a ventilated patient in circumstances in which it was clinically indicated. Importantly, for individual patients, treating clinicians will have full discretion to use whichever treatment they choose if a specific indication for PPI or H_2RB exists. This means that the study treatments carry no known additional risks compared to standard care. Once a patient recovers sufficiently to no longer require life support measures, stress ulcer prophylaxis is not indicated. In other words, in this study, participants will not be able to provide informed consent for study treatment because by the time they are competent to provide such consent, the study treatment will have ceased.

The study does not involve any specific collection of data from individual patients. Instead, the study data will be obtained from existing data sources. In essence, we believe that, in ethical terms, this study is equivalent to a very large, high quality audit of clinical practice. However, unlike a clinical practice audit in a single centre, the study design provides adequate power to detect a realistic and clinically important treatment effects. The current proposed trial will be completed rapidly and cheaply. The approach of using data from

established databases being employed in this study is novel and this trial has the potential to lay the groundwork for future trials of this type.

Given that the study poses no additional risk compared to standard treatment, we believe that it is ethically appropriate for this study to proceed with a full waiver of individual patient consent. The ethics of conducting comparative effectiveness research without individual patient consent has recently been discussed in an editorials in the *New England Journal of Medicine* and *JAMA*[41].

Because ICUs are randomised to particular treatments and full discretion is retained by treating clinicians to use either PPIs or H_2RBs for individual patients we believe that criterion #1 is met. The study poses no additional risks compared to standard treatment, and given the scale of what is proposed, could not be carried out if informed consent was required. We will protect privacy of individual patients as outlined in section 8.4.

In relation to the New Zealand *Guidelines* it is notable that the study clearly meets the *best intervention standard* and the *equipoise standard*.

We believe that a consent waiver with provision of information to study participants to inform them that this study is occurring is the most ethically appropriate approach.

In Ireland, a consent waiver approach for this study has already been approved at one site. Information will also be available to study participants to inform them that this study is occurring if requested by the local ethics committee.

For Australian participating sites an 'Opt-out approach to consent' will be applied during the conduct of this study. In line with this approach, as soon as practicable following recruitment the participant and/or their legally authorised representative will be informed of the participant's inclusion in the research and of the option to withdraw without any reduction in quality of care. If they choose to withdraw, permission will be asked to use the data collected up to that time (in accordance with the NHMRC National Statement on the Ethical Conduct of Research in Humans (March 2007) (4.4.13). Any interaction between research staff, participants and their person responsible will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relative on medical personnel provide treatment does not compromise the freedom of the decision to continue participation (Section 4.4.11 of the Statement). At each Australian participating site the Principal Investigator will be responsible for establishing a process whereby participants and visitors to the ICU will be aware of the conduct of the study. Sites will be provided with a PEPTIC generic information brochure which will be tailored for individual site details and study personnel contact information. In addition, each site will be responsible for establishing a system to ensure that all patients and/or their family receive the information about the study and how to opt out. Furthermore, all completed and signed opt-out forms will be retained as a part

of the site file and a copy of the completed form filed with the participant's medical record.

8.4 Confidentiality of patient data

The primary data repository for this study is the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database. This established registry identifies each individual patient by a unique number. This linkage between each number in the database and a particular patient is maintained by each participating hospital (i.e. data are classified as partially deidentified). Data exported from the Adult Patient Database for study analyses will not include any identifiers (i.e. the data included in the study database will be fully deidentified). The study data for patients recruited from participating Irish sites will be collected at an individual patient level and incorporated into the main study database at the end of the study. For the Irish sites a log of patient details and corresponding study number will be maintained at each site. Patients in the database will be identified by study number only.

9 DATA MANAGEMENT

9.1 Data collection methods

Site research co-ordinators will identify patients who develop a clinically significant event (*upper GI bleed or C. difficile infection*). The way of identifying these patients will be decided on at a site level, and documented in a standard operating procedure (SOP). This site-specific SOP will be used throughout the study to ensure that there is a standardised method of data collection. A copy of the SOP will be sent to the co-ordinating centre prior to the commencement of the study. The demographic data, illness severity, and in hospital mortality data used in this study will be extracted from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database. These data are routinely collected by trained ICU staff for quality assurance purposes[42]. For the Irish participants these data will be collected from individual patients.

Information about study treatments (PPIs and H_2RBs) administered to ICU patients during each of the study periods will be obtained from electronic prescribing records (in centres where these are available). We will also collect information on stress ulcer prophylaxis treatments used from medication charts on one day a month for the duration of the study.

9.2 Data management

Data management will be performed by the Australian and New Zealand Research Centre (ANZIC-RC).

10 SAFETY

10.1 Data and safety monitoring committee (DSMC)

A committee of independent experts in clinical trials, biostatistics, and intensive care medicine will be appointed to the DSMC and will review all trial protocols. The role of the DSMC will be to provide study oversight to ensure that the rights and safety of patients involved in the study are protected. A formal Charter of responsibilities of the DSMC will be prepared by the study management committee and will be signed by all of the members of the DSMC. Because the statistical power of this study depends on the crossover in an individual study ICU, an interim analysis will be underpowered. As a result, no interim analyses are planned. Given that PPIs and H_2RBs are in widespread use in current practice, it is not expected that the DSMC will advise early stopping of this study unless circumstances are exceptional. However, the DSMC may, at its absolute discretion, request assessment of any trial data at any time.

10.2 Adverse events and serious adverse events

It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgement. The baseline mortality of intensive care patients enrolled in trials will be high due to the critical illness that has necessitated their ICU admission. Intensive care patients will frequently develop life-threatening organ failure(s) unrelated to study interventions and despite optimal management. Therefore, consistent with established practice, events that are part of the natural history of the primary disease process or expected complications of critical illness will not be reported as serious adverse events in this study[43]. Additionally, events already defined and reported as study outcomes (e.g. mortality) will not be reported separately as adverse or serious adverse events unless they are considered to be causally related to the study intervention or are otherwise of concern in the investigator's judgement.

Study investigators will be actively encouraged to report all adverse reactions to PPIs and H_2RBs that occur during the study. Adverse event reporting will be in line with usual methods for reporting of suspected adverse reactions to licensed medicines. In New Zealand, suspected adverse reactions will be reported to the Centre for Adverse Reaction Monitoring (CARM)[44]. In Australia, adverse reactions will be reported using the Australian Adverse Drug Reaction Reporting System[45]. In Ireland, suspected adverse reactions will be reported according to the Health Protection Regulatory. Details of all reported adverse reactions will be provided to the DSMC.

11 STATISTICAL CONSIDERATIONS

11.1 Power calculations and sample size

Our planned sample size of approximately 25360 patients will provide 90% power to detect a 2.4% absolute difference in our composite endpoint in mechanically ventilated ICU patients. This sample size is based on a baseline composite endpoint rate of 12.0% with 40 participating ICUs enrolling an average of 317 patients per 6 month study period with a coefficient of variation of 0.60 in numbers of patients per cluster per period. It incorporates a within-cluster-within-period correlation of 0.030 and within-cluster-between-period correlation of 0.024, as observed in the ANZICS CORE Adult Patient Database in 2013 for duration of mechanical ventilation >10 days, which is the most frequent component of the composite endpoint.

11.2 Analysis plan

Analyses will be conducted on an intention-to-treat basis. Analyses of the primary composite endpoint will involve cluster (ICU) summary measures obtained by aggregating the composite endpoint to a rate per ICU per time period and calculating the difference in event rates between the first and second periods for each ICU. As outlined in Forbes et al [46], these differences will then be entered as the dependent variable into an unweighted linear regression with randomised sequence as the independent variable, from which the coefficient of the randomised sequence is then the estimated PPI versus H2RB difference. Such analyses appropriately control for all clustering effects within ICU and common secular time trends across ICUs. Uncertainty concerning treatment effects will be estimated using standard 95% confidence intervals. For secondary outcomes on a binary scale the same methods will apply, and for outcomes on a continuous scale the linear mixed model methods of Turner et al will be applied [47]. Sensitivity analyses will be performed for the impact of patients with missing outcome data using multiple imputation methods. Analyses will be performed using the Stata software package (StataCorp, Texas, USA).

11.3 Sub-groups

Pre-specified subgroups will be:

- patients who are admitted to the ICU following cardiac surgery
- emergency admissions

12 STUDY ADMINISTRATION STRUCTURE

12.1 Coordinating centre responsibilities

- Overall management of the study
- Management of study budget and liaison with funding bodies
- Protocol training for Research Co-ordinators and study team
- Preparation and arrangement of payment to sites
- Study set-up
- Organisation of investigator meetings

- Study database set-up and co-ordination of data entry

12.2 Data management centre responsibilities

- Data queries
- Data analysis

12.3 Management committee responsibilities

- Liaison with co-ordinating centre and data management centre staff
- Liaison with the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) and the Irish Critical Care Trials Group (ICCTG)
- Development and approval of the final study protocol
- General study management issues

13 FUNDING

This study is funded by the Irish Health Research Board, the Intensive Care Foundation and the Health Research Council of New Zealand

14 COST IMPLICATIONS

14.1 Overview

A 20% risk difference in *Clostridium difficile* and VAP rates attributable to using either an H_2RB or a PPI would have major cost implications for the NZ healthcare system. As outlined below, the NZ costs of ICU-acquired VAP, *Clostridium difficile*, and stress-ulcer related bleeding are in the order of $7M per year. A 20% reduction in such events would save the NZ healthcare system $1.4M per year. While ICU-acquired upper GI bleeding events probably have lower attributable cost, they still cost ≈$1M per year and differential treatment effects on the risk of these events would have important economic implications. Because the effects of PPIs and H_2RBs on infection-related and GI bleeding related complications may be opposing, we plan, depending on the findings of this study, to seek funding to undertake formal cost-effectiveness analyses once this study is completed.

14.2 Potential savings to the NZ healthcare system from infections prevented

The costs to the US healthcare of hospital acquired infections are >NZD$10 billion per year[48]. Ventilator-associated pneumonia and *Clostridium difficile* infection are the second and fourth most expensive hospital acquired infections respectively. Although there are only limited data available estimating the direct NZ healthcare costs of hospital acquired infections in NZ ICU patients, prevention of hospital-acquired infections is an identified priority for Health Safety and Quality Commission and is a potential source of major savings for the NZ healthcare system.

Among ICU patients, ventilator-associated pneumonia is the most common infection that complicates ICU admission[49]. Based on non-US data each episode of ventilator-associated pneumonia costs around NZD$12,000[50]. In

a single centre study performed at Middlemore Hospital in 2012, the average cost of treating a patient with ventilator associated pneumonia was $91,754. Over the six months of the study, the costs of the antibiotics used to treat ventilator associated pneumonia alone were $47,560. On the basis of a conservative figure of NZD$12,000 per episode and an estimated incidence of ventilator associated pneumonia of 5%, a 17-20% reduction in ventilator associated pneumonia would save the NZ healthcare system $1-1.2M per year.

According to a recent systematic review of economic healthcare costs of *Clostridium difficile*, each episode costs >NZD$6,000 (non-US data)[51]. Based on our data suggesting that 1.5% of the 10,000 patients ventilated in NZ ICUs per year develop *Clostridium difficile* infection complicating their ICU stay, this equates to a cost to NZ of $900,000 per year. A reduction in the incidence of *Clostridium difficile* cases to 1.17% of ventilated ICU patients would thus equate to a direct cost saving for NZ hospitals of between $198,000 and $330,000 per year.

14.3 Potential savings to the NZ healthcare system from GI bleeds prevented

The cost of a clinically important GI bleeding episode is estimated to be around half of that of an episode of ventilator associated pneumonia. On the basis that each episode of stress-ulcer related GI bleeding costs $6,000 and the incidence of such bleeding is 1.5%, the cost of such bleeding events is $900,000 per year. A 20% reduction in GI bleeding would save $180,000 per year.

15 PUBLICATIONS

The study will be published in the name of the study investigators, the ANZICS CTG, and the ICCTG. Dr Paul Young will be listed as the first (and corresponding) author, Prof Alistair Nichol will be the second author, Prof Rinaldo Bellomo will be the third author and other members of the management committee will be listed alphabetically. All staff at each study site who contribute to data collection will be listed as collaborators. Funding bodies will be acknowledged in the publication.

16 REFERENCES

1. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ, (2013) Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. Critical care medicine 41: 693-705
2. Aberegg SK, Richards DR, O'Brien JM, (2010) Delta inflation: a bias in the design of randomized controlled trials in critical care medicine. Crit Care 14: R77
3. Bellomo R, Forbes A, Akram M, Bailey M, Pilcher DV, Cooper DJ, (2013) Why we must cluster and cross over. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine 15: 155-157
4. Lauer MS, D'Agostino RB, Sr., (2013) The randomized registry trial--the next disruptive technology in clinical research? The New England journal of medicine 369: 1579-1581

5. Celi LA, Mark RG, Stone DJ, Montgomery RA, (2013) "Big data" in the intensive care unit. Closing the data loop. American journal of respiratory and critical care medicine 187: 1157-1160
6. Bateman BT, Bykov K, Choudhry NK, Schneeweiss S, Gagne JJ, Polinski JM, Franklin JM, Doherty M, Fischer MA, Rassen JA, (2013) Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. BMJ 347: f5416
7. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER, (2009) Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA : the journal of the American Medical Association 301: 2120-2128
8. Maclaren R, Reynolds PM, Allen RR, (2014) Histamine-2 Receptor Antagonists vs Proton Pump Inhibitors on Gastrointestinal Tract Hemorrhage and Infectious Complications in the Intensive Care Unit. JAMA internal medicine
9. Litton E EG, Bellomo R, Beasley R, Bailey MJ, Forbes AB, Gattas DJ, Pilcher DV, Webb SAR, McGuinness SP, Saxena MK, McArthur CJ, Young PJ, on behalf of the PEPTIC investigators. , (2014) A multicentre feasibility study evaluating stress ulcer prophylaxis using hospital-based registry data. . Crit Care Resus 2014 16 (in press)
10. Eastwood GM LE, Bellomo R, Bailey M, Festa M, Beasley R, Young PJ, on behalf of the PEPTIC investigators. , (2014) Intensivists' opinion and self-reported practice of stress ulcer prophylaxis in Australian and New Zealand Intensive Care Units 2014; 16:. Crit Care Resus 16 (in press)
11. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, Winton TL, Rutledge F, Todd TJ, Roy P, et al., (1994) Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. The New England journal of medicine 330: 377-381
12. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, Keus F, Guttormsen AB, Moller AD, Moller MH, (2015) Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive care medicine 41: 833-845
13. Vincent JL, (2005) Give your patient a fast hug (at least) once a day. Critical care medicine 33: 1225-1229
14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Critical care medicine 41: 580-637
15. Cohen HM, R.; Martindale, R., (2012) Guidelines for stress ulcer prophylaxis in adult critically ill patients. Society of Critical Care Medicine
16. Gratrix AP, Enright SM, O'Beirne HA, (2007) A survey of stress ulcer prophylaxis in Intensive Care Units in the UK. Anaesthesia 62: 421-422
17. Daley RJ, Rebuck JA, Welage LS, Rogers FB, (2004) Prevention of stress ulceration: current trends in critical care. Critical care medicine 32: 2008-2013
18. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M, (2014) Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients : A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive care medicine 40: 11-22
19. Klompas M, Kleinman K, Murphy MV, (2014) Descriptive epidemiology and attributable morbidity of ventilator-associated events. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 35: 502-510

20. du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A, (1982) Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. Lancet 1: 242-245
21. Netzer P, Gaia C, Sandoz M, Huluk T, Gut A, Halter F, Husler J, Inauen W, (1999) Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. The American journal of gastroenterology 94: 351-357
22. Thorens J, Froehlich F, Schwizer W, Saraga E, Bille J, Gyr K, Duroux P, Nicolet M, Pignatelli B, Blum AL, Gonvers JJ, Fried M, (1996) Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. Gut 39: 54-59
23. Kedika RR, Souza RF, Spechler SJ, (2009) Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Digestive diseases and sciences 54: 2312-2317
24. Capodicasa E, De Bellis F, Pelli MA, (1999) Effect of lansoprazole on human leukocyte function. Immunopharmacology and immunotoxicology 21: 357-377
25. Aybay C, Imir T, Okur H, (1995) The effect of omeprazole on human natural killer cell activity. General pharmacology 26: 1413-1418
26. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxbock F, Graninger W, (2002) Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. Critical care medicine 30: 1118-1122
27. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB, (2004) Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA : the journal of the American Medical Association 292: 1955-1960
28. Rodriguez LA, Ruigomez A, Wallander MA, Johansson S, (2009) Acid-suppressive drugs and community-acquired pneumonia. Epidemiology 20: 800-806
29. Miano TA, Reichert MG, Houle TT, MacGregor DA, Kincaid EH, Bowton DL, (2009) Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. Chest 136: 440-447
30. Maclaren R, Campbell J, (2014) Cost-effectiveness of histamine receptor-2 antagonist versus proton pump inhibitor for stress ulcer prophylaxis in critically ill patients*. Critical care medicine 42: 809-815
31. Leonard J, Marshall JK, Moayyedi P, (2007) Systematic review of the risk of enteric infection in patients taking acid suppression. The American journal of gastroenterology 102: 2047-2056; quiz 2057
32. Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, Toye B, Beaudoin A, Frost EH, Gilca R, Brassard P, Dendukuri N, Beliveau C, Oughton M, Brukner I, Dascal A, (2011) Host and pathogen factors for Clostridium difficile infection and colonization. The New England journal of medicine 365: 1693-1703
33. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al., (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100: 1619-1636
34. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA, (2012) Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. The New England journal of medicine
35. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ,

(2009) Intensive versus conventional glucose control in critically ill patients. The New England journal of medicine 360: 1283-1297

36. Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hebert PC, Heyland DK, Robinson BG, (2012) Hypoglycemia and risk of death in critically ill patients. The New England journal of medicine 367: 1108-1118
37. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, Kossmann T, Ponsford J, Seppelt I, Reilly P, Wolfe R, (2011) Decompressive craniectomy in diffuse traumatic brain injury. The New England journal of medicine 364: 1493-1502
38. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gardlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD, (2012) Drotrecogin alfa (activated) in adults with septic shock. The New England journal of medicine 366: 2055-2064
39. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S, (2009) Intensity of continuous renal-replacement therapy in critically ill patients. The New England journal of medicine 361: 1627-1638
40. Wennberg JE, (2002) Unwarranted variations in healthcare delivery: implications for academic medical centres. BMJ 325: 961-964
41. Faden RR, Beauchamp TL, Kass NE, (2014) Informed consent, comparative effectiveness, and learning health care. The New England journal of medicine 370: 766-768
42. Stow PJ, Hart GK, Higlett T, George C, Herkes R, McWilliam D, Bellomo R, (2006) Development and implementation of a high-quality clinical database: the Australian and New Zealand Intensive Care Society Adult Patient Database. Journal of critical care 21: 133-141
43. Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S, (2008) Serious adverse events in academic critical care research. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 178: 1181-1184
44. Monitoring CfAR (2014). In: Editor (ed)^(eds) Book., City, pp.
45. System AADRR, (2014)
46. Forbes A AM, Pilcher D, Cooper J, Bellomo R, (2014) Cluster randomised crossover trials with binary data and unbalanced cluster sizes: applications to studies of near-universal interventions in intensive care.
47. Turner RM, White IR, Croudace T, (2007) Analysis of cluster randomized cross-over trial data: a comparison of methods. Statistics in medicine 26: 274-289
48. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, Keohane C, Denham CR, Bates DW, (2013) Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA internal medicine 173: 2039-2046
49. Safdar N, Dezfulian C, Collard HR, Saint S, (2005) Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Critical care medicine 33: 2184-2193
50. Muscedere JG, Martin CM, Heyland DK, (2008) The impact of ventilator-associated pneumonia on the Canadian health care system. Journal of critical care 23: 5-10
51. Ghantoji SS, Sail K, Lairson DR, DuPont HL, Garey KW, (2010) Economic healthcare costs of Clostridium difficile infection: a systematic review. The Journal of hospital infection 74: 309-318

CLINICAL TRIAL PROTOCOL

Proton Pump Inhibitors vs. Histamine-2 REceptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC)

A multi-centre, cluster randomised, crossover, registry trial comparing the safety and efficacy of proton pump inhibitors with histamine-2 receptor blockers for ulcer prophylaxis in intensive care patients requiring invasive mechanical intervention

Protocol Version: Version 3.1
21 August 2019

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Funding: Health Research Council, New Zealand (15/649)
Health Research Board, Ireland

ABBREVIATIONS

ANZICS = Australian and New Zealand Intensive Care Society
CTG = Clinical Trials Group
GI = Gastrointestinal
H_2RB = Histamine-2 receptor blocker
ICU = Intensive Care Unit
M-H = Mantel Haenszel
PPI = proton pump inhibitor
SUP = stress ulcer prophylaxis

1 GENERAL INFORMATION

1.1 Title

A multi-centre, cluster randomised, crossover, registry trial comparing the safety and efficacy of proton pump inhibitors with histamine-2 receptor blockers for ulcer prophylaxis in intensive care unit patients requiring invasive mechanical ventilation.

1.2 Chief investigator

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1.4 Participating centres

50 ICUs from Australia, Canada, New Zealand, Ireland, and the United Kingdom.

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2 LAY SUMMARY

2.1 Stress ulcers in the Intensive Care Unit

Patients who require treatment in the Intensive Care Unit (ICU) can develop stomach ulcers or duodenal (small intestine) ulcers. This occurs most commonly when life support (a breathing machine) is required or when the patient develops a bleeding tendency as a result of their illness. These kinds of ulcers are known as 'stress ulcers' and may cause life-threatening bleeding.

2.2 Prevention of stress ulcers in the Intensive Care Unit

Patients who require life support in the ICU are typically given one of two types of medicine to try and prevent the development of stress ulcers. The two types of medicines are called 'proton pump inhibitors' (PPIs) and 'histamine-2 receptor blockers' (H_2RBs). While the prevention of stress ulcers is very important, the medicines used to prevent ulcers may have important side effects including an increased risk of developing certain kinds of infections. The risk of side effects may depend on the medication used.

2.3 Purpose of the study

This study will establish which of the two types of medicines that are commonly used for stress ulcer prophylaxis in ICU patients who require life support leads to the lowest risk of upper gastrointestinal bleeding, prolonged mechanical ventilation, and *Clostridium difficile* infection.

2.4 Study design

The study will use a design known as a 'cluster crossover registry design'. In this type of study, data are collected primarily from existing data sources rather than the medical records of individual patients. There will be two study treatment periods. During the first treatment period, half of the participating ICUs will be randomly (like the toss of a coin) instructed to use PPIs for stress ulcer prophylaxis in patients who require life-support while the other half will use H_2RBs. During the second treatment period each ICU will swap to using the opposite treatment. This means that, in situations where PPIs and H_2RBs are regarded as being equivalent by the treating clinician, the treatment administered to the patients will be determined based on the treatment assigned to the patient's ICU. However, if there is a specific indication for either PPI treatment or H_2RB treatment (for example, an allergy), the treatment indicated for the particular patient concerned will be administered irrespective of the treatment assigned to the ICU. In other words, in this study, all patients will receive the treatment that the treating clinician believes to be in their best interests irrespective of the default treatment assigned to the ICU.

2.5 Study importance

This study will enrol >15 times as many patients as have been studied in all previous clinical trials comparing approaches to stress ulcer prophylaxis in the ICU combined[1]. The study will provide robust estimates of the relative risk

of clinically significant upper gastrointestinal (GI) bleeding and complications that are potentially related to using PPIs vs. H_2RBs for stress ulcer prophylaxis, a treatment currently given to an estimated 2.5 million ICU patients per year in developed countries alone.

In addition to the direct clinical benefit of comparing stress ulcer treatments, the study utilises an innovative design that has the potential to revolutionise the conduct of clinical trials both in the ICU and in other areas of medicine. Compared with current standard parallel group RCTs, a 'cluster crossover' trial using existing data sources to obtain data provides the opportunity to efficiently detect small, but clinically important, treatment effects rapidly and for comparatively lower cost.

3 SYNOPSIS

Overview	Multi-centre, cluster crossover, randomised trial comparing proton pump inhibitors (PPIs) with histamine-2 receptor blockers (H_2RBs) for ulcer prophylaxis in mechanically ventilated ICU patients.
Design	Cluster crossover trial using registry data.
Participants	All patients aged ≥18 years mechanically ventilated within 24 hours of ICU admission except for those whose ICU admission diagnosis is upper GI bleeding.
Intervention	Study treatment is open label PPIs vs. H_2RBs as the default routine therapy for ulcer prophylaxis. Each study ICU will use PPIs or H_2RBs as routine therapy for a period of six months. At the end of this six month period, the ICU will then swap to the opposite routine ulcer prophylaxis strategy which will then be used for the next six months. Study treatment will only be administered in situations where the treating clinician believes ulcer prophylaxis is in the patient's best interests and, irrespective of the treatment assigned to the ICU, either a PPI or an H_2RB can be used for an individual patient, if the treating clinician believes that a particular treatment is indicated.
Primary end point	In hospital mortality (censored at 90 days)
Secondary end points	1. Upper gastrointestinal bleeding The cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU. Clinically significant upper GI bleed is defined as: overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or visualised by upper GI endoscopy) AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic,

	mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in haemoglobin of at least 20 g/L, or 4) transfusion of 2 units of packed red blood cells or more). 2. *Clostridium difficile* infections. Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients in whom a positive specimen was collected prior to ICU admission) 3. ICU length of stay per patient 4. Hospital length of stay per patient 5. Ventilation hours (where applicable)
Statistical considerations and sample size	With 50 ICUs, and assuming a baseline mortality of 15%, our study will have 80% power to detect a 2.4% absolute difference in in-hospital mortality at a 5% significance. This sample size is based on input parameters estimated from the ANZICS APD administrative data, with an average of 310 admissions per site in each 6-month study period with a variation in number of admissions of 0.50, and incorporates a within-cluster–within-period correlation of 0.035 and within-cluster–between-period correlation of 0.025.

4 BACKGROUND AND RATIONALE

4.1 The 'cluster crossover registry trial'.

One of the factors responsible for the large number of negative trials in the field of intensive care medicine is that 'effect sizes' attributable to treatments being tested are often exaggerated[2]. One of the problems investigators face is that conducting a conventional randomised controlled trial (RCT) with a large enough sample size to detect realistic treatment effects is generally prohibitive in terms of both logistics and cost. Instead, we propose an innovative study design combining two novel trial methodologies: cluster crossover randomisation[3] and collection of outcome data from existing data sources[4]. This design offers the dual prospect of generating the statistical power necessary to evaluate candidate interventions with small effect sizes and of being much cheaper than a conventional RCT because it uses data that are already collected for other purposes.

The cluster crossover design will randomise entire ICUs rather than individual patients. Each ICU will define a cluster and each ICU will cross over to use both of the treatment approaches being tested by the end of the study. Existing registry data sources will be used to collect baseline, intervention, and outcome data for the patients admitted to the study ICUs during the trial. Recent academic discourse has highlighted the potential for 'big data' to advance medical knowledge[5] but the idea of performing a large scale randomised trial relying on multiple existing data sources is a new innovation in clinical research. In addition to being innovative, we contend that this is also the optimal trial design for testing ubiquitous ICU interventions where the necessary data are already being collected for quality assurance and other purposes, and where clinical equipoise exists for testing two accepted treatment regimens. This methodology has the potential to revolutionise the conduct of clinical trials in the ICU and in other areas of medicine. In the ICU there are many interventions that could be tested using this approach in the future.

4.2 The cluster crossover registry trial and the choice of stress ulcer prophylaxis

The type of stress ulcer prophylaxis used in the ICU is a logical choice for the initial intervention to test in a cluster crossover registry trial because:

1. Published RCTs lack adequate power to confirm or refute the existence of clinically important treatment effects suggested by observation studies[1], [6-8]
2. An adequately powered traditional parallel-group RCT would be prohibitively costly to perform
3. Existing data sources can be used to collect clinically important outcomes [9]
4. The use of PPIs or H_2RBs for stress ulcer prophylaxis is a common ICU intervention and the best agent to use is uncertain[10]
5. There is a strong biological rationale for believing that the choice of stress ulcer prophylaxis influences clinically important outcomes

4.3 Comparative effectiveness of PPIs and H_2RBs for stress ulcer prophylaxis

4.3.1 Upper GI bleeding

4.3.1.1 The importance of upper GI bleeding in the ICU

In a prospective multicentre cohort study conducted in 1994, clinically important upper gastrointestinal haemorrhage occurred in 1.5% (95% CI; 1.0-2.1%) of ICU patients. The mortality rate was 48.5 percent in the group with bleeding and 9.1 percent in the group without bleeding ($P < 0.001$)[11]. We have recently shown that, across seven tertiary ICUs in Australia and New Zealand, the median percentage per ICU of patients with new upper GI bleeding complicating ICU admission is 1.4% (IQR 0.3-1.8)[9] and a large, high quality, international observational cohort study demonstrated an incidence of 2.5%[12].

4.3.1.2 Stress ulcer prophylaxis in the ICU

The perceived importance of stress ulcer prophylaxis is highlighted by its incorporation into quality-oriented checklists for the care of the critically ill such as the FASTHUG mnemonic where the letter 'U' stands for ulcer prophylaxis[13]. There is uncertainty about which type of ulcer prophylaxis is preferred. The Surviving Sepsis Campaign guidelines recommend the use of PPIs[14] while the Society of Critical Care Medicine recommend H_2RBs[15]. In a recently conducted survey, ICU specialists from Australia and New Zealand estimated that, in their ICUs, an average of 84% of ventilated patients receive stress ulcer prophylaxis[10]. This is in agreement with a recently, conducted survey of ICU specialists from Ireland, of whom 85% give ventilated patients stress ulcer prophylaxis, 80-100% of the time (personal communication-AN). As is the case in other parts of the world[16, 17] PPIs and H_2RBs are the most common medicines given for stress ulcer prophylaxis in Australia[9, 10]. Irish Intensivists use PPI 83% of the time and H_2RBs 13% of the time (n=91) when administering SUP personal communication-AN).

4.3.1.3 The risk of upper GI bleeding with PPIs vs. H_2RBs

Overall, PPIs may be more effective at reducing upper GI bleeding than H_2RBs[1]. In a recent systematic review and meta-analysis comparing PPIs with H_2RBs for ulcer prophylaxis in the ICU, fourteen trials enrolling 1,720 patients reported an end point of overt upper gastrointestinal bleeding. The use of PPI resulted in a significantly lower risk of overt bleeding than the use of H_2RB (RR 0.35; 95% CI 0.21-0.59; $P<0.0001$; $I^2 = 15\%$) (see Figure 2)[1]. Although these data constitute level I evidence that PPIs are more effective at reducing upper GI bleeding than H_2RBs, possible publication bias and weaknesses in trial methodology mean that there remains uncertainty about this apparent difference[1]. Paradoxically, recent data suggest that PPIs might actually be associated with an increased risk of clinically significant bleeding in the ICU population compared to H_2RBs[9, 15].

Figure 1 Forest plot for overt upper gastrointestinal bleeding for stress ulcer prophylaxis vs. placebo. Data from 14 trials were included in the analysis using random effects model. M-H: Mantel Haenszel; SUP: Stress Ulcer Prophylaxis. Reproduced from Krag et al[18]

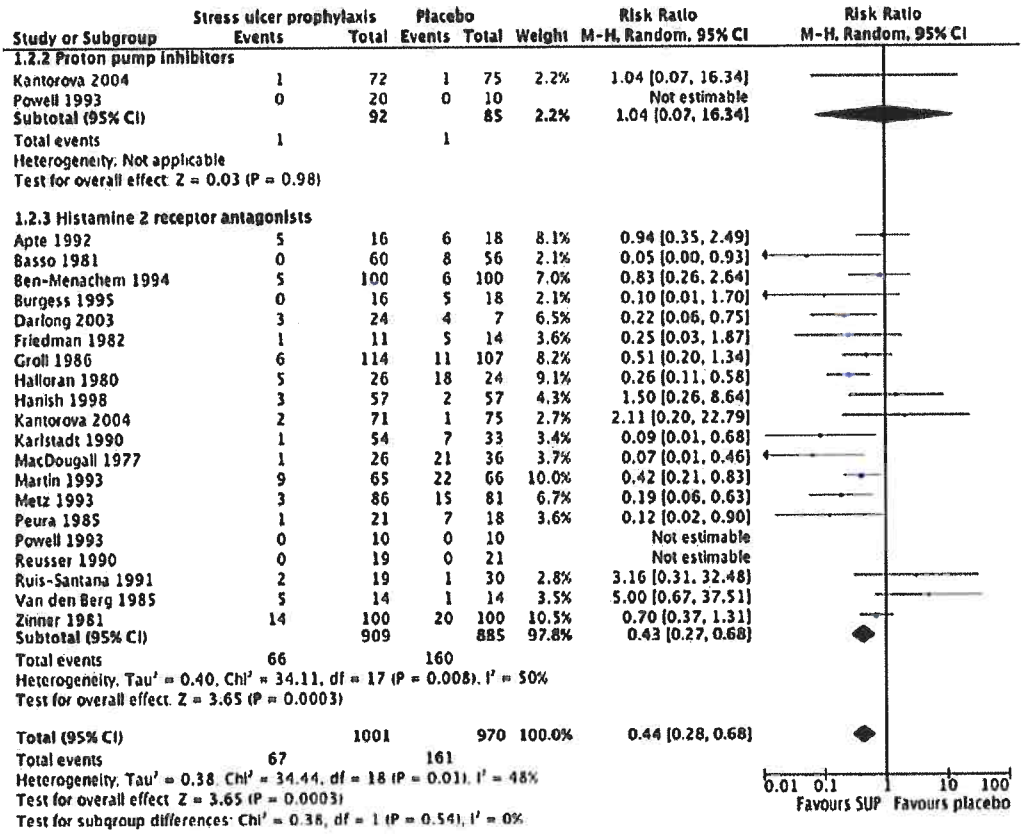
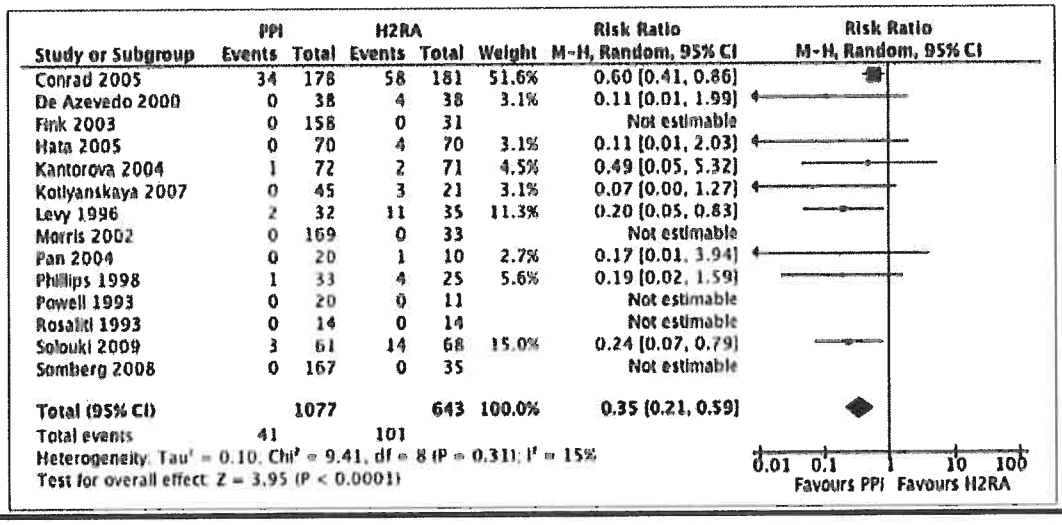


Figure 2 Forest plot for overt upper gastrointestinal bleeding outcome. Data from 14 trials were included in the analysis using random effects model. M-H Mantel Haenszel. reproduced from Alhazzani et al[1]



4.3.2 Hospital acquired pneumonia

4.3.2.1 The importance of hospital acquired pneumonia in the ICU

Hospital acquired infections including pneumonia are associated with prolonged hospital stays, increased health care resource utilisation, and increased mortality risk[19].

4.3.2.2 The biological basis by which choice of ulcer prophylaxis may influence pneumonia risk

The aspiration of gastric bacteria is a frequent source of airway colonisation and appears to have a pathophysiological role in the development of pneumonia in ICU patients. In ventilated ICU patients, the number of Gram negative bacilli in gastric aspirates increases as the gastric pH increases[20]. PPIs cause more profound acid suppression[21] and lead to significantly more bacterial overgrowth of the stomach and duodenum than H_2RBs[22].

In addition to promoting bacterial overgrowth, PPIs appear to exert a range of immunosuppressive effects[23]. For example, lansoprazole induces significant inhibition of human natural killer cell activity, reduces polymorphonuclear cell chemotaxis, and decreases superoxide generation[24]. Omeprazole also inhibits natural killer cells suggesting that that the suppression of natural killer cell function is a class effect of PPIs[25]. Similarly, in healthy volunteers, a single 40mg dose of omeprazole leads to a reduction in neutrophil reactive oxygen production and reduces neutrophil bactericidal capacity by 30%[26]. While the clinical significance of the immunosuppressive effects of PPIs is uncertain, these data lend weight to the hypothesis that using PPIs for ulcer prophylaxis rather than H_2RBs might increase pneumonia risk.

4.3.2.3 Observational studies comparing the pneumonia risk of patients treated with PPIs vs. H_2RBs

In the community setting, use of acid-suppressive medicines appears to be a risk factor for the subsequent development of pneumonia[27]. PPIs are associated with a greater pneumonia risk than H_2RBs and a significant positive dose-response relationship for pneumonia risk is present among PPI users[27]. Emphasising the potential differential risk associated with the choice of medication for ulcer prophylaxis, a case-control series comparing 7297 patients with pneumonia with 9993 matched controls, showed that the relative risk of newly diagnosed community-acquired pneumonia was increased with current use of PPIs (RR = 1.16 [95% confidence interval 1.03-1.31]) but not with the use of H_2RBs (0.98 [0.80-1.20])[28]. Similarly, in a cohort study including 63,878 hospital admissions (but excluding patients requiring ICU admission) the incidence of hospital-acquired pneumonia was higher in the patients exposed to acid-suppressive medication than in the unexposed group (4.9% vs 2.0%; odds ratio [OR], 2.6; 95% confidence interval [CI], 2.3-2.8). In this study, after multivariate logistic regression, the association between acid suppressive medications and pneumonia risk was significant for PPIs (OR, 1.3; 95% CI, 1.1-1.4) but not for H_2RBs (OR, 1.2; 95% CI, 0.98-1.4)[7].

In the ICU setting, PPI use is associated with increased pneumonia risk compared to H_2RB use. In a 35,312-patient retrospective cohort study of

adults requiring mechanical ventilation for 24 hours or more and administered either an H_2RB or PPI for 48 hours or more while intubated, pneumonia occurred in 38.6% of PPI-treated patients vs. 27% of H_2RB-treated patients (P<0.001)[8]. Using propensity score adjusted multivariate regression modelling to control for confounders, PPI use was associated with a significantly increased risk of pneumonia compared to H_2RB use (OR 1.2; 95% CI 1.03-1.41)[8]. Similarly, in a single centre retrospective study of cardiothoracic surgical patients, treatment with a PPI was found to be associated with a markedly elevated risk of nosocomial pneumonia (OR 6.6; 95% CI 2.9 to 14.9)[29]. After propensity adjusted, multivariable logistic regression, PPI treatment was found to be an independent risk factor for nosocomial pneumonia (adjusted OR 2.7, 95% CI 1.1-6.7) compared to H_2RB treatment[29]. These findings were subsequently replicated in a larger multicentre retrospective cohort study published recently in the *BMJ* (see Table 1)[6].

Table 1 Relative risk of postoperative pneumonia in patients undergoing coronary artery bypass graft surgery treated with PPI compared with H_2RB (reproduced from Bateman et al[6])

	No of outcomes/No of patients			
Analysis	**PPI**	**H2RA**	**Risk ratio (95% CI)**	**Risk difference (95% CI) per 1000 patients**
Unadjusted	492/9830	487/11 384	1.17 (1.04 to 1.32)	7.3 (1.6 to 13.0)
Age, sex, race, calendar year adjusted	492/9830	487/11 384	1.19 (1.04 to 1.36)	—
Propensity score tenths stratified	411/8514	421/10 059	1.19 (1.03 to 1.38)	—
Propensity score matched	369/7537	323/7537	1.14 (0.99 to 1.32)	6.1 (−0.6 to 12.8)

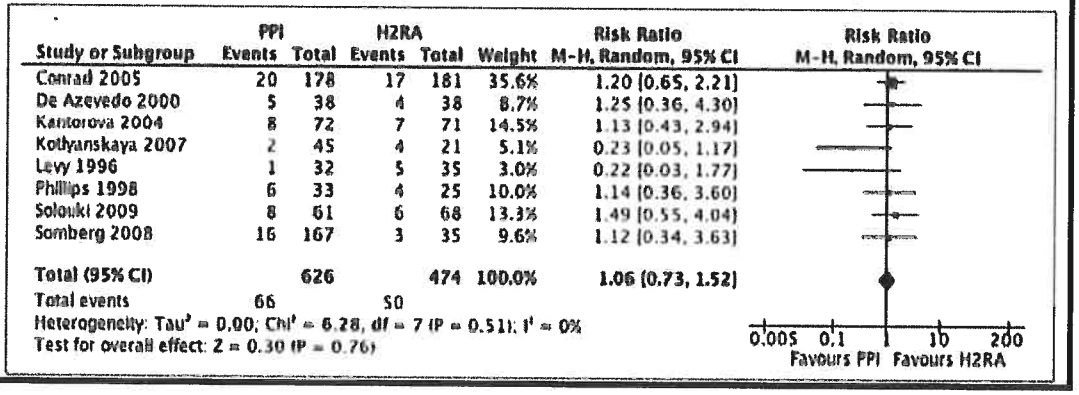
In this study, patients undergoing coronary artery bypass graft surgery who received prophylaxis with PPIs had an increased risk of postoperative pneumonia compared to patients treated with H_2RBs (OR 1.17; 95% CI 1.04 to 1.32)[6]. This risk remained after adjustment for confounding factors using multiple analytic approaches.

Overall, observational data support the hypothesis that using a PPI instead of an H_2RB for stress ulcer prophylaxis in the ICU predisposes patients to developing hospital-acquired pneumonia.

4.3.2.4 Randomised controlled trials comparing the pneumonia risk of patients treated with PPIs vs. H_2RBs

A recent meta-analysis of randomised controlled trials comparing PPIs with H_2RBs in critically ill patients identified only eight trials, enrolling a total of 1,100 patients, reporting the acquisition of nosocomial pneumonia as an outcome variable (see Figure 3)[1].

Figure 3 Forrest plot for nosocomial pneumonia risk in ICU patients receiving PPI vs H2RB for ulcer prophylaxis (RR 1.06; 95% CI 0.73-1.52); M-H: Mantel Haenszel; PPI proton pump inhibitor) reproduced from Alhazzani et al[1].



Even when combined in a meta-analysis, the available sample is inadequate to provide the statistical power necessary to detect the small but potentially very important increase in pneumonia risk with PPI use suggested by the observational data. Indeed, estimates of precision for the relative risk of pneumonia with PPIs vs. H2RBs do not exclude the possibility that PPI use increases the risk of hospital-acquired pneumonia by 50% compared to using H2RBs. The most appropriate conclusion to draw from the current randomised controlled trial data is that studies with adequate power have not been performed. Recent data highlight that any differential effect of PPIs vs. H2RBs on pneumonia risk is likely to be the greatest determinant of the relative cost-effectiveness of these medicines[30].

4.3.2.5 Summary

There is a substantial body of literature supporting the hypothesis that the choice of medication administered for ulcer prophylaxis affects the risk of developing pneumonia in ICU patients. Observational trials suggest that use of PPIs may increase the risk of developing pneumonia by 20% compared to H2RBs. The existing evidence-base from randomised controlled trials is insufficient to exclude an effect of this magnitude.

4.3.3 Clostridium difficile infection

No randomised trials of PPIs vs. H2RBs have reported *Clostridium difficile* colitis as an outcome measure. However, a systematic review of 12 observational studies evaluating 2,948 patients found that the development of *Clostridium difficile* infection was associated with the use of PPIs and H2RBs[31]. The association for PPI use was greater (OR 2.05; 95% CI 1.47-2.85) than for H2RB use (OR 1.47; 95% CI 1.06-2.05) although, the difference in the strength of the association was not significant[31]. A recent prospective *NEJM* study designed to identify host and pathogen risk factors for *Clostridium difficile* infection and colonisation showed that PPI-use was associated with an increased risk of health-care associated *Clostridium difficile* infection (OR 2.64; 95% CI 1.71-4.09) but that H2RB use was not (OR 0.98; 95% CI 0.55-4.09)[32]. In a recent cohort study evaluating 35,312 adult patients from 71 hospitals requiring mechanical ventilation for ≥24 hours and administered an H2RB or PPI for ≥48 hours while intubated, use of PPIs

instead of H_2RBs was independently associated with an increased risk of *Clostridium difficile* infection (OR 1.29; 95%CI 1.04-1.64)[8]. Overall, any differential effect of PPIs and H_2RBs on the incidence of *Clostridium difficile* colitis is uncertain. However, it is biologically plausible that the type of ulcer prophylaxis alters the risk of developing this important complication.

4.4 Summary of the background

PPIs and H_2RBs are both used commonly for stress ulcer prophylaxis in Australia, New Zealand, Ireland, and in other parts of the world. However, the relatively small number of subjects who have been studied in randomised trials limits the existing trial data comparing PPIs and H_2RBs for ulcer prophylaxis in the ICU. It appears that the choice between a PPI and a H_2RB for ulcer prophylaxis may alter a patient's risk of developing upper GI bleeding, pneumonia, and *Clostridium difficile* infection. Clinical trials of adequate size to determine the magnitude of any risk differences have not been performed and are a high priority given the widespread use of these medicines.

5 OBJECTIVES

The overall objective of this study is ***to determine the safety and efficacy of using PPIs vs. H_2RBs for routine ulcer prophylaxis in mechanically ventilated patients in the ICU.***

Specifically, the study will compare, between treatment groups:

1. The risk of in-hospital mortality (censored at 90 days)
2. The risk of developing clinically significant upper gastrointestinal bleeding.
3. The risk of developing an infection with *Clostridium difficile* while in ICU.
4. The ICU and hospital length of stay.
5. Ventilation hours (where applicable)

6 STUDY DESIGN

6.1 General

This study is a randomised, multicentre, multinational, cluster cross over registry trial designed to establish the safety and efficacy of using PPIs vs. H_2RBs as the routine strategy for ulcer prophylaxis in mechanically ventilated ICU patients. The study will be divided into two treatment periods of six months. During the first treatment period, half of the ICUs will use PPIs for routine ulcer prophylaxis while the other half of the ICUs will use H_2RBs. During the second treatment period, each ICU will use the opposite treatment strategy. The treatment order will be randomised.

6.2 Study centre eligibility criteria

6.2.1 Inclusion criteria

1. Any non-paediatric ICU that routinely manages mechanically ventilated patients will potentially be eligible to participate in the study.

6.2.2 Exclusion criteria

1. ICUs that are unable or unwilling to follow the trial protocol, or
2. ICUs that are unable to capture the required study data

6.3 Individual patient eligibility criteria

6.3.1 Inclusion criteria

1. Patients aged 18 years or older who are invasively mechanically ventilated within the first 24 hours of an ICU admission.

6.3.2 Exclusion criteria

1. Patients who are admitted to ICU with upper GI bleeding (APACHE III admission diagnostic codes 303, 305, and 1403)

6.4 Baseline data

The following baseline data will be collected from the ANZICS-CORE Adult Patient Database (or using a case report form in the sites in Ireland):

- Age
- Gender
- Admission type (elective vs. emergency)
- ICU admission source (i.e. ED vs. ward vs. theatre vs. other hospital)
- Chronic APACHE co-morbidities
- APACHE-III admission diagnosis[33]
- Illness severity based on the APACHE-II and III scores and risk of death, and "ANZ Risk of Death" models score[33]

6.5 Study treatments

This study is designed to compare two *approaches* to ulcer prophylaxis in the ICU. It will compare the open label use of PPIs with the use of H_2RBs as the default therapy for ulcer prophylaxis. The treating clinician will be able to use either a PPI or an H_2RB in rare situations where a particular treatment is clearly preferable. Patients who are usually taking a PPI or an H_2RB will switch to the treatment strategy assigned to the ICU for the duration of their ICU stay unless the treating clinician believes that this is inappropriate for the particular patient being treated. If overt upper gastrointestinal bleeding occurs, then a PPI will be administered in accordance with standard clinical practice, irrespective of treatment allocation.

While study treatment (PPI or H_2RB) will be administered for ulcer prophylaxis at the discretion of the treating clinician, routine administration of study treatment to patients receiving mechanical ventilation is expected to occur in line with current standard care[10]. The duration of study treatment will be until death, ICU discharge, or until the treating clinician no longer believes

ulcer prophylaxis is indicated. The total amount of PPI and H_2RB dispensed in each of the study ICUs will be collected for each of the study periods. Once a month, at a set time, each participating ICU will record the number of ventilated patients in the ICU receiving a PPI, the number of ventilated patients receiving an H_2RB, and the number of ventilated patients who are not receiving any stress ulcer prophylaxis. At the same time point, we will also collect the same data limited to the patients who are ventilated and on their second day in ICU (i.e. the day after ICU admission). In participating ICUs with electronic prescribing records the proportion of study patients in each treatment period who receive PPI or H_2RB and the total average dose will be recorded.

6.6 Treatment allocation

At the beginning of the study, half of the study ICUs will be randomly assigned to using H_2RBs for routine ulcer prophylaxis while the other half will be assigned routinely using PPIs. During the second treatment period ICUs will crossover to the opposite treatment. The order in which ICUs use the treatments will be determined by an independent statistician using a computer algorithm.

6.7 Outcome measures

Censoring of all study end points will apply at the time of hospital discharge following the index ICU admission or at 90 days (whichever is earlier).

6.7.1 Primary outcome measure

The primary outcome measure is in-hospital all cause mortality (censored at day 90).

6.7.2 Secondary outcome measures

6.7.2.1 Upper gastrointestinal bleeding

The principal end point of interest in relation to upper GI bleeding is the cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU. Clinically significant upper GI bleed is defined as: overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or upper GI endoscopy) AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in hemoglobin of at least 20 g/L or 4) transfusion of 2 units of packed red blood cells or more).

6.7.2.2 *Clostridium difficile* infection rates

The specific end point which will be reported in relation to *Clostridium difficile* infection rates is the:

- Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients who had positive tests from specimens collected prior to ICU admission)

6.7.2.3 ICU length of stay

6.7.2.4 Hospital length of stay

6.7.2.5 Ventilation hours (where applicable)

7 FEASIBILITY

The ICUs in Australia, New Zealand and Ireland involved in the study have an established research infrastructure and have participated in a number of large scale studies leading to a number of recent NEJM publications[34-39]. We have completed a multicentre, multinational, feasibility study demonstrating that practice varies between ICUs in Australia and New Zealand[9], and Ireland (personal communication [AN]). In this study, which included seven ICUs, we were able to collect information from databases and registries on dispensing PPIs and H_2RBs, episodes of GI bleeding, *Clostridium difficile* infections, and respiratory tract colonisation with pathogenic organisms[9]. Our data confirm that collection of the outcomes relevant to an interventional trial of stress ulcer prophylaxis in the ICU using only existing data sources is feasible in a cohort of Australian, New Zealand, and Irish ICUs[9]. Furthermore, in recent surveys of ICU specialists from Australia and New Zealand and Ireland the majority of respondents (89% and 79% respectively) indicated that their belief was that there was currently insufficient evidence to determine the optimal medicine for stress ulcer prophylaxis in ICU patients and there was broad agreement that a large-scale comparative effectiveness trial is required[10].

The statistical team at the Australian and New Zealand Intensive Care Research Centre, who will conduct the statistical analyses, are familiar with the data being used in the study. The study will be co-ordinated from the MRINZ which has extensive experience in conducting similar multicentre RCTs including the 0.9% Saline vs. PlasmaLyte 148 for ICU fluid Therapy (SPLIT) trial (ACTRN12613001370796), a large-scale cluster crossover trial using individual patient data collection methods.

8 ETHICS

8.1 Guiding principles

This study is to be performed in accordance with *World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects* (WMA 2008), the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2002), the *ICH Harmonised Tripartite Guideline: Guideline for good clinical practice* (ICH 1996), the WHO *Ethical issues in Patient Safety Research: Interpreting existing guidance* (WHO 2013), and the New Zealand Health and Disability Ethics Committee *Ethical Guidelines for Interventional Studies (the Guidelines)*.

8.2 Legal issues in this study

This trial will be conducted in compliance with relevant New Zealand (NZ) legislation including the Health Information Privacy Code, the Health and Disability Code and the NZ Bill of Rights (NZBOR) Act. This trial does not

involve 'experimental' interventions. Instead, it evaluates 'standard treatments' in a systematic way in order to allow clinicians to understand how to best care for critically ill patients in the future.

8.3 Ethical issues in this study

Patterns of practice in different hospitals are often idiosyncratic and unscientific[40]. Indeed, much of clinical medicine remains empirical and local medical opinion and supply of resources are often more important than science in determining how medical care is delivered[40]. Wide variations that characterise usual clinical practice often have no basis in science but may have important implications for patient outcomes. Where there are two distinct approaches without clear evidence that one approach or the other is superior, we believe that there is an ethical imperative to conduct research to establish which approach is best.

All patients enrolled in this trial will lack capacity to give consent at the time stress ulcer prophylaxis is administered. In usual clinical practice stress ulcer prophylaxis is administered to non-consenting ICU patients as part of routine treatment because administration of stress ulcer prophylaxis is considered to be in the patient's best interest. In this study all patients with a clinical indication for stress ulcer prophylaxis will receive one of two standard treatments (PPI or H_2RB for ulcer prophylaxis). Stress ulcer prophylaxis is one of many treatments which are considered to be part of routine ICU care and is typically not specifically discussed with patients or their relatives. We do not consider that it would be ethically appropriate to withhold stress ulcer prophylaxis from a ventilated patient in circumstances in which it was clinically indicated. Importantly, for individual patients, treating clinicians will have full discretion to use whichever treatment they choose if a specific indication for PPI or H_2RB exists. This means that the study treatments carry no known additional risks compared to standard care. Once a patient recovers sufficiently to no longer require life support measures, stress ulcer prophylaxis is not indicated. In other words, in this study, participants will not be able to provide informed consent for study treatment because by the time they are competent to provide such consent, the study treatment will have ceased.

The study does not involve any specific collection of data from individual patients. Instead, the study data will be obtained from existing data sources. In essence, we believe that, in ethical terms, this study is equivalent to a very large, high quality audit of clinical practice. However, unlike a clinical practice audit in a single centre, the study design provides adequate power to detect a realistic and clinically important treatment effects. The current proposed trial will be completed rapidly and cheaply. The approach of using data from established databases being employed in this study is novel and this trial has the potential to lay the groundwork for future trials of this type.

Given that the study poses no additional risk compared to standard treatment, we believe that it is ethically appropriate for this study to proceed with a full waiver of individual patient consent. The ethics of conducting comparative effectiveness research without individual patient consent has recently been discussed in an editorials in the *New England Journal of Medicine* and *JAMA*[41].

Because ICUs are randomised to particular treatments and full discretion is retained by treating clinicians to use either PPIs or H_2RBs for individual patients we believe that criterion #1 is met. The study poses no additional risks compared to standard treatment, and given the scale of what is proposed, could not be carried out if informed consent was required. We will protect privacy of individual patients as outlined in section 8.4.

In relation to the New Zealand *Guidelines* it is notable that the study clearly meets the *best intervention standard* and the *equipoise standard*.

We believe that a consent waiver with provision of information to study participants to inform them that this study is occurring is the most ethically appropriate approach.

In Ireland, a consent waiver approach for this study has already been approved at one site. Information will also be available to study participants to inform them that this study is occurring if requested by the local ethics committee.

For Australian participating sites an 'Opt-out approach to consent' will be applied during the conduct of this study. In line with this approach, as soon as practicable following recruitment the participant and/or their legally authorised representative will be informed of the participant's inclusion in the research and of the option to withdraw without any reduction in quality of care. If they choose to withdraw, permission will be asked to use the data collected up to that time (in accordance with the NHMRC National Statement on the Ethical Conduct of Research in Humans (March 2007) (4.4.13). Any interaction between research staff, participants and their person responsible will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relative on medical personnel provide treatment does not compromise the freedom of the decision to continue participation (Section 4.4.11 of the Statement). At each Australian participating site the Principal Investigator will be responsible for establishing a process whereby participants and visitors to the ICU will be aware of the conduct of the study. Sites will be provided with a PEPTIC generic information brochure which will be tailored for individual site details and study personnel contact information. In addition, each site will be responsible for establishing a system to ensure that all patients and/or their family receive the information about the study and how to opt out. Furthermore, all completed and signed opt-out forms will be retained as a part of the site file and a copy of the completed form filed with the participant's medical record.

8.4 Confidentiality of patient data

The primary data repository for this study is the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database. This established registry identifies each individual patient by a unique number. This linkage between each number in the database and a particular patient is maintained by each participating hospital (i.e. data are

classified as partially deidentified). Data exported from the Adult Patient Database for study analyses will not include any identifiers (i.e. the data included in the study database will be fully deidentified). The study data for patients recruited from participating Irish sites will be collected at an individual patient level and incorporated into the main study database at the end of the study. For the Irish sites a log of patient details and corresponding study number will be maintained at each site. Patients in the database will be identified by study number only.

9 DATA MANAGEMENT

9.1 Data collection methods

Site research co-ordinators will identify patients who develop a clinically significant event (*upper GI bleed or C. difficile infection*). The way of identifying these patients will be decided on at a site level, and documented in a standard operating procedure (SOP). This site-specific SOP will be used throughout the study to ensure that there is a standardised method of data collection. A copy of the SOP will be sent to the co-ordinating centre prior to the commencement of the study. The demographic data, illness severity, and in hospital mortality data used in this study will be extracted from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database. These data are routinely collected by trained ICU staff for quality assurance purposes[42]. For the Irish participants these data will be collected from individual patients.

Information about study treatments (PPIs and H_2RBs) administered to ICU patients during each of the study periods will be obtained from electronic prescribing records (in centres where these are available). We will also collect information on stress ulcer prophylaxis treatments used from medication charts on one day a month for the duration of the study.

9.2 Data management

Data management will be performed by the Australian and New Zealand Research Centre (ANZIC-RC).

10 SAFETY

10.1 Data and safety monitoring committee (DSMC)

A committee of independent experts in clinical trials, biostatistics, and intensive care medicine will be appointed to the DSMC and will review all trial protocols. The role of the DSMC will be to provide study oversight to ensure that the rights and safety of patients involved in the study are protected. A formal Charter of responsibilities of the DSMC will be prepared by the study management committee and will be signed by all of the members of the DSMC. Because the statistical power of this study depends on the crossover in an individual study ICU, an interim analysis will be underpowered. As a result, no interim analyses are planned. Given that PPIs and H_2RBs are in widespread use in current practice, it is not expected that the DSMC will advise early stopping of this study unless circumstances are exceptional.

However, the DSMC may, at its absolute discretion, request assessment of any trial data at any time.

10.2 Adverse events and serious adverse events

It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgement. The baseline mortality of intensive care patients enrolled in trials will be high due to the critical illness that has necessitated their ICU admission. Intensive care patients will frequently develop life-threatening organ failure(s) unrelated to study interventions and despite optimal management. Therefore, consistent with established practice, events that are part of the natural history of the primary disease process or expected complications of critical illness will not be reported as serious adverse events in this study[43]. Additionally, events already defined and reported as study outcomes (e.g. mortality) will not be reported separately as adverse or serious adverse events unless they are considered to be causally related to the study intervention or are otherwise of concern in the investigator's judgement.

Study investigators will be actively encouraged to report all adverse reactions to PPIs and H_2RBs that occur during the study. Adverse event reporting will be in line with usual methods for reporting of suspected adverse reactions to licensed medicines. In New Zealand, suspected adverse reactions will be reported to the Centre for Adverse Reaction Monitoring (CARM)[44]. In Australia, adverse reactions will be reported using the Australian Adverse Drug Reaction Reporting System[45]. In Ireland, suspected adverse reactions will be reported according to the Health Protection Regulatory. Details of all reported adverse reactions will be provided to the DSMC.

11 STATISTICAL CONSIDERATIONS

11.1 Power calculations and sample size

With 50 ICUs, and assuming a baseline mortality of 15%, our study will have 80% power to detect a 2.4% absolute difference in in-hospital mortality at a 5% significance. This sample size is based on input parameters estimated from the ANZICS APD administrative data, with an average of 310 admissions per site in each 6-month study period with a variation in number of admissions of 0.50, and incorporates a within-cluster–within-period correlation of 0.035 and within-cluster–between-period correlation of 0.025.

11.2 Analysis plan

Analyses will be conducted on an intention-to-treat basis. Analyses of the primary end point will involve cluster (ICU) summary measures obtained by aggregating the primary endpoint to a rate per ICU per time period and calculating the difference in event rates between the first and second periods for each ICU. As outlined in Forbes et al [46], these differences will then be

entered as the dependent variable into an unweighted linear regression with randomised sequence as the independent variable, from which the coefficient of the randomised sequence is then the estimated PPI versus H2RB difference. Such analyses appropriately control for all clustering effects within ICU and common secular time trends across ICUs. Uncertainty concerning treatment effects will be estimated using standard 95% confidence intervals. For secondary outcomes on a binary scale the same methods will apply, and for outcomes on a continuous scale the linear mixed model methods of Turner et al will be applied [47]. Sensitivity analyses will be performed for the impact of patients with missing outcome data using multiple imputation methods. Analyses will be performed using the Stata software package (StataCorp, Texas, USA).

11.3 Sub-groups

Pre-specified subgroups will be:

- patients who are admitted to the ICU following cardiac surgery
- emergency admissions

12 STUDY ADMINISTRATION STRUCTURE

12.1 Coordinating centre responsibilities

- Overall management of the study
- Management of study budget and liaison with funding bodies
- Protocol training for Research Co-ordinators and study team
- Preparation and arrangement of payment to sites
- Study set-up
- Organisation of investigator meetings
- Study database set-up and co-ordination of data entry

12.2 Data management centre responsibilities

- Data queries
- Data analysis

12.3 Management committee responsibilities

- Liaison with co-ordinating centre and data management centre staff
- Liaison with the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) and the Irish Critical Care Trials Group (ICCTG)
- Development and approval of the final study protocol
- General study management issues

13 FUNDING

This study is funded by the Irish Health Research Board, the Intensive Care Foundation and the Health Research Council of New Zealand

14 COST IMPLICATIONS

14.1 Overview

A 20% risk difference in *Clostridium difficile* and VAP rates attributable to using either an H_2RB or a PPI would have major cost implications for the NZ healthcare system. As outlined below, the NZ costs of ICU-acquired VAP, *Clostridium difficile*, and stress-ulcer related bleeding are in the order of $7M per year. A 20% reduction in such events would save the NZ healthcare system $1.4M per year. While ICU-acquired upper GI bleeding events probably have lower attributable cost, they still cost ≈$1M per year and differential treatment effects on the risk of these events would have important economic implications. Because the effects of PPIs and H_2RBs on infection-related and GI bleeding related complications may be opposing, we plan, depending on the findings of this study, to seek funding to undertake formal cost-effectiveness analyses once this study is completed.

14.2 Potential savings to the NZ healthcare system from infections prevented

The costs to the US healthcare of hospital acquired infections are >NZD$10 billion per year[48]. Ventilator-associated pneumonia and *Clostridium difficile* infection are the second and fourth most expensive hospital acquired infections respectively. Although there are only limited data available estimating the direct NZ healthcare costs of hospital acquired infections in NZ ICU patients, prevention of hospital-acquired infections is an identified priority for Health Safety and Quality Commission and is a potential source of major savings for the NZ healthcare system.

Among ICU patients, ventilator-associated pneumonia is the most common infection that complicates ICU admission[49]. Based on non-US data each episode of ventilator-associated pneumonia costs around NZD$12,000[50]. In a single centre study performed at Middlemore Hospital in 2012, the average cost of treating a patient with ventilator associated pneumonia was $91,754. Over the six months of the study, the costs of the antibiotics used to treat ventilator associated pneumonia alone were $47,560. On the basis of a conservative figure of NZD$12,000 per episode and an estimated incidence of ventilator associated pneumonia of 5%, a 17-20% reduction in ventilator associated pneumonia would save the NZ healthcare system $1-1.2M per year.

According to a recent systematic review of economic healthcare costs of *Clostridium difficile*, each episode costs >NZD$6,000 (non-US data)[51]. Based on our data suggesting that 1.5% of the 10,000 patients ventilated in NZ ICUs per year develop *Clostridium difficile* infection complicating their ICU stay, this equates to a cost to NZ of $900,000 per year. A reduction in the incidence of *Clostridium difficile* cases to 1.17% of ventilated ICU patients would thus equate to a direct cost saving for NZ hospitals of between $198,000 and $330,000 per year.

14.3 Potential savings to the NZ healthcare system from GI bleeds prevented

The cost of a clinically important GI bleeding episode is estimated to be around half of that of an episode of ventilator associated pneumonia. On the basis that each episode of stress-ulcer related GI bleeding costs $6,000 and the incidence of such bleeding is 1.5%, the cost of such bleeding events is $900,000 per year. A 20% reduction in GI bleeding would save $180,000 per year.

15 PUBLICATIONS

The study will be published in the name of the study investigators, the ANZICS CTG, and the ICCTG. Dr Paul Young will be listed as the first (and corresponding) author, Prof Alistair Nichol will be the second author, Prof Rinaldo Bellomo will be the third author and other members of the management committee will be listed alphabetically. All staff at each study site who contribute to data collection will be listed as collaborators. Funding bodies will be acknowledged in the publication.

16 REFERENCES

1. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ, (2013) Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. Critical care medicine 41: 693-705
2. Aberegg SK, Richards DR, O'Brien JM, (2010) Delta inflation: a bias in the design of randomized controlled trials in critical care medicine. Crit Care 14: R77
3. Bellomo R, Forbes A, Akram M, Bailey M, Pilcher DV, Cooper DJ, (2013) Why we must cluster and cross over. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine 15: 155-157
4. Lauer MS, D'Agostino RB, Sr., (2013) The randomized registry trial--the next disruptive technology in clinical research? The New England journal of medicine 369: 1579-1581
5. Celi LA, Mark RG, Stone DJ, Montgomery RA, (2013) "Big data" in the intensive care unit. Closing the data loop. American journal of respiratory and critical care medicine 187: 1157-1160
6. Bateman BT, Bykov K, Choudhry NK, Schneeweiss S, Gagne JJ, Polinski JM, Franklin JM, Doherty M, Fischer MA, Rassen JA, (2013) Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. BMJ 347: f5416
7. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER, (2009) Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA : the journal of the American Medical Association 301: 2120-2128
8. Maclaren R, Reynolds PM, Allen RR, (2014) Histamine-2 Receptor Antagonists vs Proton Pump Inhibitors on Gastrointestinal Tract Hemorrhage and Infectious Complications in the Intensive Care Unit. JAMA internal medicine
9. Litton E EG, Bellomo R, Beasley R, Bailey MJ, Forbes AB, Gattas DJ, Pilcher DV, Webb SAR, McGuinness SP, Saxena MK, McArthur CJ, Young PJ, on behalf of the PEPTIC investigators. , (2014) A multicentre feasibility study evaluating stress ulcer prophylaxis using hospital-based registry data. . Crit Care Resus 2014 16 (in press)
10. Eastwood GM LE, Bellomo R, Bailey M, Festa M, Beasley R, Young PJ, on behalf of the PEPTIC investigators. , (2014) Intensivists' opinion and self-reported

practice of stress ulcer prophylaxis in Australian and New Zealand Intensive Care Units 2014; 16:. Crit Care Resus 16 (in press)

11. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, Winton TL, Rutledge F, Todd TJ, Roy P, et al., (1994) Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. The New England journal of medicine 330: 377-381
12. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, Keus F, Guttormsen AB, Moller AD, Moller MH, (2015) Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive care medicine 41: 833-845
13. Vincent JL, (2005) Give your patient a fast hug (at least) once a day. Critical care medicine 33: 1225-1229
14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Critical care medicine 41: 580-637
15. Cohen HM, R.; Martindale, R., (2012) Guidelines for stress ulcer prophylaxis in adult critically ill patients. Society of Critical Care Medicine
16. Gratrix AP, Enright SM, O'Beirne HA, (2007) A survey of stress ulcer prophylaxis in Intensive Care Units in the UK. Anaesthesia 62: 421-422
17. Daley RJ, Rebuck JA, Welage LS, Rogers FB, (2004) Prevention of stress ulceration: current trends in critical care. Critical care medicine 32: 2008-2013
18. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M, (2014) Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients : A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive care medicine 40: 11-22
19. Klompas M, Kleinman K, Murphy MV, (2014) Descriptive epidemiology and attributable morbidity of ventilator-associated events. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 35: 502-510
20. du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A, (1982) Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. Lancet 1: 242-245
21. Netzer P, Gaia C, Sandoz M, Huluk T, Gut A, Halter F, Husler J, Inauen W, (1999) Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. The American journal of gastroenterology 94: 351-357
22. Thorens J, Froehlich F, Schwizer W, Saraga E, Bille J, Gyr K, Duroux P, Nicolet M, Pignatelli B, Blum AL, Gonvers JJ, Fried M, (1996) Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. Gut 39: 54-59
23. Kedika RR, Souza RF, Spechler SJ, (2009) Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Digestive diseases and sciences 54: 2312-2317
24. Capodicasa E, De Bellis F, Pelli MA, (1999) Effect of lansoprazole on human leukocyte function. Immunopharmacology and immunotoxicology 21: 357-377
25. Aybay C, Imir T, Okur H, (1995) The effect of omeprazole on human natural killer cell activity. General pharmacology 26: 1413-1418
26. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxbock F, Graninger W, (2002) Omeprazole treatment diminishes intra- and extracellular neutrophil

reactive oxygen production and bactericidal activity. Critical care medicine 30: 1118-1122

27. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB, (2004) Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA : the journal of the American Medical Association 292: 1955-1960
28. Rodriguez LA, Ruigomez A, Wallander MA, Johansson S, (2009) Acid-suppressive drugs and community-acquired pneumonia. Epidemiology 20: 800-806
29. Miano TA, Reichert MG, Houle TT, MacGregor DA, Kincaid EH, Bowton DL, (2009) Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. Chest 136: 440-447
30. Maclaren R, Campbell J, (2014) Cost-effectiveness of histamine receptor-2 antagonist versus proton pump inhibitor for stress ulcer prophylaxis in critically ill patients*. Critical care medicine 42: 809-815
31. Leonard J, Marshall JK, Moayyedi P, (2007) Systematic review of the risk of enteric infection in patients taking acid suppression. The American journal of gastroenterology 102: 2047-2056; quiz 2057
32. Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, Toye B, Beaudoin A, Frost EH, Gilca R, Brassard P, Dendukuri N, Beliveau C, Oughton M, Brukner I, Dascal A, (2011) Host and pathogen factors for Clostridium difficile infection and colonization. The New England journal of medicine 365: 1693-1703
33. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al., (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100: 1619-1636
34. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA, (2012) Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. The New England journal of medicine
35. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ, (2009) Intensive versus conventional glucose control in critically ill patients. The New England journal of medicine 360: 1283-1297
36. Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hebert PC, Heyland DK, Robinson BG, (2012) Hypoglycemia and risk of death in critically ill patients. The New England journal of medicine 367: 1108-1118
37. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, Kossmann T, Ponsford J, Seppelt I, Reilly P, Wolfe R, (2011) Decompressive craniectomy in diffuse traumatic brain injury. The New England journal of medicine 364: 1493-1502
38. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gardlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD, (2012) Drotrecogin alfa (activated) in adults with septic shock. The New England journal of medicine 366: 2055-2064
39. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S, (2009) Intensity of continuous renal-replacement therapy in critically ill patients. The New England journal of medicine 361: 1627-1638

40. Wennberg JE, (2002) Unwarranted variations in healthcare delivery: implications for academic medical centres. BMJ 325: 961-964
41. Faden RR, Beauchamp TL, Kass NE, (2014) Informed consent, comparative effectiveness, and learning health care. The New England journal of medicine 370: 766-768
42. Stow PJ, Hart GK, Higlett T, George C, Herkes R, McWilliam D, Bellomo R, (2006) Development and implementation of a high-quality clinical database: the Australian and New Zealand Intensive Care Society Adult Patient Database. Journal of critical care 21: 133-141
43. Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S, (2008) Serious adverse events in academic critical care research. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 178: 1181-1184
44. Monitoring CfAR (2014). In: Editor (ed)^(eds) Book., City, pp.
45. System AADRR, (2014)
46. Forbes A AM, Pilcher D, Cooper J, Bellomo R, (2014) Cluster randomised crossover trials with binary data and unbalanced cluster sizes: applications to studies of near-universal interventions in intensive care.
47. Turner RM, White IR, Croudace T, (2007) Analysis of cluster randomized cross-over trial data: a comparison of methods. Statistics in medicine 26: 274-289
48. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, Keohane C, Denham CR, Bates DW, (2013) Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA internal medicine 173: 2039-2046
49. Safdar N, Dezfulian C, Collard HR, Saint S, (2005) Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Critical care medicine 33: 2184-2193
50. Muscedere JG, Martin CM, Heyland DK, (2008) The impact of ventilator-associated pneumonia on the Canadian health care system. Journal of critical care 23: 5-10
51. Ghantoji SS, Sail K, Lairson DR, DuPont HL, Garey KW, (2010) Economic healthcare costs of Clostridium difficile infection: a systematic review. The Journal of hospital infection 74: 309-318

17 VERSION HISTORY

Version 1.1 dated 11th March 2015 – approved by HDEC 14th April 2015

Version 2.0 dated 24th November 2015 – approved by HDEC 21st March 2016

Version 3.0 dated 25th August 2016 – approved by HDEC 05th April 2017

Version 3.0 of the protocol was made country specific in the UK. The country specific version is:

Version 1.1 dated 3rd January 2018 (UK specific protocol)

Version 3.1 dated 21st August 2019 – Current protocol

Summary of Changes Document:

Proton Pump Inhibitors vs. Histamine-2 REceptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC)

Version change

Version 2.0 (24 November 2015) to 3.1 (21 August 2019)

UTN: U1111-1151-5142

ANZCTRN: ANZCTR 12616000481471

Investigators:

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Section	Original Text	New Text	Reason/Justification of Change
Version 2.0 (24 November 2015) to 3.0 (25 August 2016)			
Title page (ANZCTRN)	pending	ANZCTR 12616000481471	Trial now registered with the Australian New Zealand Clinical Trials Registry
1.4 Participating centres	Participating centres have not yet been confirmed; however, the following centres have expressed interest in this study: • Armadale Hospital • Auckland City Hospital (Department of Critical care Medicine) • Auckland City Hospital (Cardiovascular Intensive Care Unit) • Austin Hospital • Alfred Hospital • Bendigo Hospital • Bunbury Hospital • Canberra Hospital • Christchurch Hospital • Concord Hospital • Freemantle Hospital • Geelong Hospital • Gold Coast University Hospital • Hawkes Bay Hospital • Liverpool • Middlemore Hospital	40 ICUs from Australia, New Zealand, Ireland and United Kingdom	We have elected not to list individual site names as all sites have not been confirmed and we wish to avoid further protocol amendments if possible

	• Nepean Hospital • Northern Hospital • North Shore Hospital • Princess Alexandra Hospital • Queen Elizabeth Hospital • Royal Hobart Hospital • Royal Melbourne Hospital • Royal North Shore Hospital • Royal Prince Alfred Hospital • Royal Perth Hospital • Sir Charles Gairdner • St Vincent's Melbourne • St Vincent's Hospital, Sydney • St Vincent's University Hospital, Dublin (& at least six other Irish ICUs) • Tauranga Hospital • St George Hospital • Wellington Hospital • Western Hospital • Whangarei Hospital • Wollongong Hospital		

3 Synopsis (Participants)	All mechanically ventilated patients aged ≥18 years except for those whose ICU admission diagnosis is upper GI bleeding	All patients aged ≥18 years mechanically ventilated within 24 hours of ICU admission except for those whose ICU admission diagnosis is upper GI bleeding	Reworded for clarification
3 Synopsis (Primary end point)	Major complications arising during the ICU admission (censored at 90 days), using a composite end point comprising the following: (i) clinically significant upper GI bleeding (ii) *Clostridium difficile* infections (iii) episodes of mechanical ventilation of more than 10 days	In hospital mortality (censored at 90 days)	Mortality is generally considered to be the gold standard outcome measure in critically ill patients. We have made this change because we consider that this outcome captures the overall balance of risks and benefits of each study treatment best.
3 Synopsis (Secondary end points)	1. In hospital mortality (censored at 90 days) 2. Upper gastrointestinal bleeding The principal end point of interest in relation to upper GI bleeding is the cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU. Clinically significant upper GI bleed is defined as: overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or visualised by upper GI endoscopy)	1. Upper gastrointestinal bleeding The cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU. Clinically significant upper GI bleed is defined as: overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or visualised by upper GI endoscopy) AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in	This change reflects the fact that mortality is now the primary end point.

	AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in haemoglobin of at least 20 g/L, or 4) transfusion of 2 units of packed red blood cells or more). 3. *Clostridium difficile* infections. Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients in whom a positive specimen was collected prior to ICU admission) 4. Hours of mechanical ventilation per patient 5. ICU length of stay per patient 6. Hospital length of stay per patient	vasopressor dose 3) decrease in haemoglobin of at least 20 g/L, or 4) transfusion of 2 units of packed red blood cells or more). 2. *Clostridium difficile* infections. Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients in whom a positive specimen was collected prior to ICU admission) 3. ICU length of stay per patient 4. Hospital length of stay per patient 5. Ventilation hours (where applicable)	
3 Synopsis (Statistical consideration	Our planned sample size of approximately 25360 patients will provide 90% power to	With 40 ICUs and assuming a baseline mortality of 15% our study will have 80% power to	Changing the primary end point has necessitated a change in the power calculations.

and sample size)	detect a 2.4% absolute difference in our composite endpoint. This sample size is based on a baseline composite endpoint rate of 12.0% with 40 participating ICUs enrolling an average of 317 patients per 6 month study period with a coefficient of variation of 0.60 in numbers of patients per cluster per period. It incorporates a within-cluster-within-period correlation of 0.030 and within-cluster-between-period correlation of 0.024, as observed in the ANZICS CORE Adult Patient Database in 2013 for duration of mechanical ventilation > 10 days, which is the most frequent component of the composite endpoint.	detect a 2.7% absolute difference in in-hospital mortality. This sample size is based on an average of 310 admissions per site in each 6 month study period. It incorporates a within-cluster-within-period correlation of 0.035 and within-cluster-between-period correlation of 0.025.	
5 Objectives	The overall objective of this study is ***to establish the number of complications which occur using PPIs vs. H_2RBs for routine ulcer prophylaxis in mechanically ventilated patients in the ICU using a composite end point consisting of: (i) clinically significant upper gastrointestinal bleeding, (ii) prolonged mechanical***	The overall objective of this study is ***to determine the safety and efficacy of using PPIs vs. H_2RBs for routine ulcer prophylaxis in mechanically ventilated patients in the ICU.***	We have revised the overall objective to make it clearer and simpler.

	ventilation, and, (iii) Clostridium difficile infection.		
5 Objectives	In addition, the study will establish the relative efficacy and safety of using PPIs vs. H_2RBs in the mechanically ventilated patients in ICU with respect to: 1. The risk of in-hospital mortality (censored at 90 days) 2. The risk of developing clinically significant upper gastrointestinal bleeding. 3. The risk of developing an infection with *Clostridium difficile* while in ICU. 4. Duration of mechanical ventilation. 5. ICU and hospital length of stay.	Specifically, the study will compare, between treatment groups: 1. The risk of in-hospital mortality (censored at 90 days) 2. The risk of developing clinically significant upper gastrointestinal bleeding. 3. The risk of developing an infection with *Clostridium difficile* while in ICU. 4. The ICU and hospital length of stay. 5. Ventilation hours (where applicable)	Reworded to make it simpler.
6.3.1 Inclusion criteria	1. Patients aged 18 years or older who are invasively mechanically ventilated at any time during an ICU admission.	2. Patients aged 18 years or older who are invasively mechanically ventilated within the first 24 hours of an ICU admission.	Reworded for clarification
6.4 Baseline data	The following baseline data will be collected from the ANZICS-CORE Adult Patient Database: • Age • Gender	The following baseline data will be collected from the ANZICS-CORE Adult Patient Database **(or using a case report form in the sites in Ireland):**	Irish sites do not have a database where we can extract the demographic data, illness severity and in hospital mortality data and this will be collected from individual patients.

	• Admission type (elective vs emergency) • ICU admission source (i.e. ED vs ward vs theatre vs other hospital) • Chronic APACHE co-morbidities • APACHE-III admission diagnosis [33] • Illness severity based on the on the APACHE-II and III scores and risk of death, and "ANZ Risk of Death" models score [33]	• Age • Gender • Admission type (elective vs emergency) • ICU admission source (i.e. ED vs ward vs theatre vs other hospital) • Chronic APACHE co-morbidities • APACHE-III admission diagnosis [33] Illness severity based on the APACHE-II and III scores and risk of death, and "ANZ Risk of Death" models score [33]	
6.4 Baseline data	• Illness severity based on the on the APACHE-II and III scores and risk of death, and "ANZ Risk of Death" models score [33]	• Illness severity based ~~on~~ ~~the~~ on the APACHE-II and III scores and risk of death, and "ANZ Risk of Death" models score [33]	Correction of typographical error
6.7.1 Primary outcome measure	The primary outcome measure is a composite end point comprising the cumulative incidence of the following complications: • Clinically significant upper GI bleeding • *Clostridium difficile* infections • Episodes of mechanical ventilation of more than 10 days.	The primary outcome measure is in-hospital all cause mortality (censored at day 90).	See previous comments above

6.7.2 Secondary outcome measures	6.7.2.1 In-hospital all cause mortality (Censored at day 90). 6.7.2.2 Upper gastrointestinal bleeding The principal end point of interest in relation to upper GI bleeding is the cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU. Clinically significant upper GI bleed is defined as: overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or upper GI endoscopy) AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in hemoglobin of at least 20 g/L or 4) transfusion of	6.7.2.1 Upper gastrointestinal bleeding The principal end point of interest in relation to upper GI bleeding is the cumulative incidence of patients with new *clinically significant upper GI bleeding* developing as a complication in ICU. Clinically significant upper GI bleed is defined as: overt GI bleeding (eg. haematemesis, malaena or frank blood in the nasogastric tube or upper GI endoscopy) AND ≥1 of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in hemoglobin of at least 20 g/L or 4) transfusion of 2 units of packed red blood cells or more). 6.7.2.2 *Clostridium difficile* infection rates The specific end point which will be reported in relation to *Clostridium difficile* infection rates is the: • Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-	See previous comments above

	2 units of packed red blood cells or more). 6.7.2.3 *Clostridium difficile* infection rates The specific end point which will be reported in relation to *Clostridium difficile* infection rates is the: • Cumulative incidence of patients with *Clostridium difficile* toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients who had positive tests from specimens collected prior to ICU admission) 6.7.2.4 Hours of mechanical ventilation 6.7.2.5 ICU length of stay 6.7.2.6 Hospital length of stay	positive stool samples collected during an ICU admission (excluding any patients who had positive tests from specimens collected prior to ICU admission) 6.7.2.3 ICU length of stay 6.7.2.4 Hospital length of stay 6.7.2.5 Ventilation hours (where applicable)	
11.1 Power calculations and sample size	Our planned sample size of approximately 25360 patients will provide 90% power to detect a 2.4% absolute difference in our composite endpoint in mechanically ventilated ICU patients. This	With 40 ICUs and assuming a baseline mortality of 15% our study will have 80% power to detect a 2.7% absolute difference in in-hospital mortality. This sample size is based on an average of 310	See previous comments above

	sample size is based on a baseline composite endpoint rate of 12.0% with 40 participating ICUs enrolling an average of 317 patients per 6 month study period with a coefficient of variation of 0.60 in numbers of patients per cluster per period. It incorporates a within-cluster-within-period correlation of 0.030 and within-cluster-between-period correlation of 0.024, as observed in the ANZICS CORE Adult Patient Database in 2013 for duration of mechanical ventilation >10 days, which is the most frequent component of the composite endpoint.	admissions per site in each 6 month study period. It incorporates a within-cluster-within-period correlation of 0.035 and within-cluster-between-period correlation of 0.025.	
11.2 Analysis plan	Analyses of the primary composite endpoint will involve cluster (ICU) summary measures obtained by aggregating the composite endpoint to a rate per ICU per time period and calculating the difference in event rates between the first and second periods for each ICU.	Analyses of the primary end point will involve cluster (ICU) summary measures obtained by aggregating the primary end point to a rate per ICU per time period and calculating the difference in event rates between the first and second periods for each ICU.	This change reflects the change in the primary end point outline above.
Version 3.0 (25 August 2016) to 3.1 (21 August 2019)			
1.3 Investigators	Michael Bailey Richard Beasley	Sean Bagshawe Michael Bailey	Added investigators from Canada and United Kingdom

	Rinaldo Bellomo Glenn Eastwood Marino Festa Andrew Forbes David Gattas Frank Van Haren Ed Litton Diane Mackle Colin McArthur Shay McGuinness Alistair Nichol David Pilcher Manoj Saxena Steve Webb	Richard Beasley Rinaldo Bellomo Glenn Eastwood Marino Festa Andrew Forbes David Gattas Frank van Haren Ed Litton Diane Mackle Colin McArthur Shay McGuinness Paul Mouncey Alistair Nichol David Pilcher Manoj Saxena Steve Webb Stephen Wright	
1.4 Participating centres	40 ICUs from Australia, New Zealand, Ireland and United Kingdom	50 ICUs from Australia, Canada, New Zealand, Ireland and the United Kingdom	• Total participating sites of 50 ICUs • Added Canada
3 Synopsis (Statistical considerations and sample size)	With 40 ICUs and assuming a baseline mortality of 15% our study will have 80% power to detect a 2.7% absolute difference in in-hospital mortality. This sample size is based on an average of 310 admissions per site in each 6 month study period. It incorporates a within-cluster-within-period correlation of 0.035 and within-cluster-between-period correlation of 0.025.	With 50 ICUs, and assuming a baseline mortality of 15%, our study will have 80% power to detect a 2.4% absolute difference in in-hospital mortality at a 5% significance. This sample size is based on input parameters estimated from the ANZICS APD administrative data, with an average of 310 admissions per site in each 6-month study period with a variation in number of admissions of 0.50, and incorporates a within-	An updated calculation based on the total number of participating sites.

		cluster–within-period correlation of 0.035 and within-cluster–between-period correlation of 0.025.	
11.1 Power calculations and sample size	With 40 ICUs and assuming a baseline mortality of 15% our study will have 80% power to detect a 2.7% absolute difference in in-hospital mortality. This sample size is based on an average of 310 admissions per site in each 6 month study period. It incorporates a within-cluster-within-period correlation of 0.035 and within-cluster-between-period correlation of 0.025.	With 50 ICUs, and assuming a baseline mortality of 15%, our study will have 80% power to detect a 2.4% absolute difference in in-hospital mortality at a 5% significance. This sample size is based on input parameters estimated from the ANZICS APD administrative data, with an average of 310 admissions per site in each 6-month study period with a variation in number of admissions of 0.50, and incorporates a within-cluster–within-period correlation of 0.035 and within-cluster–between-period correlation of 0.025.	An updated calculation based on the total number of participating sites.
17 Version History	Not available in previous protocol	Version 1.1 dated 11th March 2015 – approved by HDEC 14th April 2015 Version 2.0 dated 24th November 2015 – approved by HDEC 21st March 2016 Version 3.0 dated 25th August 2016 – approved by HDEC 05th April 2017	Version history of the study and a description of a different version which is country specific to UK.

		Version 3.0 of the protocol was made country specific in the UK. The country specific version is: Version 1.1 dated 3rd January 2018 (UK specific protocol) Version 3.1 dated 21st August 2019 – Current protocol	

Statistical analysis plan for the PEPTIC study (version 1)

Posted online on the 30th of September 2019 (prior to locking the database)

The PEPTIC management committee members are Paul J Young, Sean M Bagshaw, Alistair Nichol, Stephen E Wright, Rinaldo Bellomo, Richard W Beasley, Glenn M Eastwood, Marino Festa, David Gattas, Frank van Haren, Edward Litton, Paul R Mouncey, Leanlove Navarra, David Pilcher, Diane Mackle, Colin J McArthur, Shay P McGuinness, Manoj K. Saxena, Steve Webb, and Kathryn M Rowan.

The study statisticians are Andrew Forbes and Michael J Bailey.

PEPTIC is endorsed by the Australia and New Zealand Intensive Care Society Clinical Trials Group, the Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group. The study is supported by the Australian and New Zealand Intensive Care – Research Centre, the Irish Critical Care Trials Network, the Medical Research Institute of New Zealand, the United Kingdom Intensive Care National Audit & Research Centre, and the United Kingdom Critical Care Research Group.

OUTCOME DEFINITIONS

Primary Outcome

The primary outcome is in-hospital all-cause mortality up to 90 days from the date of the index ICU admission. All patients discharged prior to 90 days and who survive the index hospital admission will be considered as alive at 90 days. In-hospital mortality is recorded in all of the registries that are being used as the primary data source for the PEPTIC study.

Secondary Outcomes

1. Clinically significant upper GI bleeding:

Defined as overt upper GI bleeding (e.g. haematemesis, melaena or frank blood in the nasogastric tube or upper GI endoscopy) developing as a complication in the ICU and accompanied by one or more of the following features within 24 hours of overt upper GI bleeding:

i. A spontaneous drop of systolic, diastolic, or mean arterial pressure ≥20 mmHg
ii. Initiation of a vasopressor or a 20% increase in ongoing vasopressor dose
iii. A decrease in haemoglobin of ≥20 g/L
iv. A transfusion of at least two units of packed red blood cells

2. *C. difficile* infection:

Defined as a patient who has a new *C. difficile* toxin or culture-positive stool sample collected during an ICU admission (excluding any patients who had positive tests from specimens collected prior to ICU admission).

3. ICU length of stay

Defined as the time between ICU admission and ICU discharge for the index ICU admission (i.e. it excludes ICU readmission time and time spent in a second or subsequent ICU).

4. Hospital length of stay

Defined as the time between ICU admission and index hospital discharge (i.e. it excludes any time spent in hospital if readmitted).

Tertiary Outcome

1. Duration of mechanical ventilation:

Defined as the total hours of invasive mechanical ventilation during the index ICU admission. This includes any re-ventilation periods following initial weaning during the index ICU admission. For patients enrolled in the United Kingdom, duration of mechanical ventilation will be determined from the number of

calendar days (00:00 to 23:59) on which advanced respiratory support is received, because the United Kingdom database does not collect the number of hours of invasive mechanical ventilation. For patients who received advanced respiratory support on one calendar day, the total hours of invasive mechanical ventilation will be assumed to be 12. For patients who received advanced respiratory support on more than one calendar day, the total number of hours of invasive mechanical ventilation will be assumed to be 12 hours on the first day of advanced respiratory support, 12 hours on the last day of advanced respiratory support, and 24 hours on the intermediary days (i.e. the total number of hours of invasive ventilation will be calculated as the number of calendar days of advanced respiratory support minus one calendar day multiplied by 24 hours). If the total number of hours of invasive mechanical ventilation calculated by this method exceeds the total number of hours the patient spent in the ICU, the number of hours of mechanical ventilation will be truncated to equal the total hours the patient spend in the ICU. We anticipate that duration of mechanical ventilation will not be recorded in all participants / sites because collection of this variable was not mandatory in all sites at the time the study was conducted.

2. Ventilator-associated conditions

Defined as events where, after a period of stability or improvement on invasive mechanical ventilation of at least two days, a patient has at least one of the following indicators of worsening oxygenation:

i. An increase in daily minimum FIO_2 of ≥0.20 over the daily minimum FIO_2 in the baseline period of stability, sustained for at least two days;
ii. An increase in daily minimum positive end expiratory pressure (PEEP) values of at least three cmH_2O over the daily minimum PEEP in the baseline period, sustained for at least two days (daily minimum defined by lowest FIO_2 or PEEP during a calendar day that is maintained for at least one hour)

The ventilator-associated conditions Outcome is available only for Canadian sites because data to derive this variable is not included in the registry databases from other countries.

STATISTICAL ANALYSES

Principles

Each patient will be included in the study only once so in the event that a patient is readmitted to hospital or the ICU after the initial qualifying ICU admission (index ICU admission), data that pertain to the second and any subsequent ICU or hospital admissions will not be included in the database. Analyses will be conducted on an intention-to-treat basis, meaning that all patients will be analysed according to the randomised treatment of their ICU at the time of the index ICU admission, regardless of treatment actually received. Descriptive statistics at ICU level will be presented by allocated treatment sequence, and patient characteristics will be summarised by allocated treatment sequence and observation period (see Table 1 and Tables S1 and S2 below).

Primary Outcome: in-hospital all-cause mortality up to 90 days from the date of the index ICU admission

Comparison of randomised treatment groups will use individual patient-level data and generalised estimating equations (GEE) with a logarithmic link function, an exchangeable working correlation matrix and robust standard errors using the ICU as the clustering unit. Because randomisation was performed in batches of ICUs, covariate adjustment for randomisation batch, the order of administration of the treatments, and batch-by-order interaction will be performed to allow for separate order/secular time effects occurring in each of the randomisation batches. Because the number of patients receiving each treatment will not be exactly equal within each ICU, the treatment effect will be partitioned into its within-ICU and between-ICU components by including the proportion of patients receiving treatment A in each ICU (which may be H_2RB or PPI) as a covariate together with the treatment group[1]. The within-ICU treatment effect estimate, not confounded by differences between ICUs and represented by the main effect of treatment arm in these models, will be reported. The effect of treatment comparisons will be presented as risk ratio and 95% confidence from the GEE analysis, and as a risk difference and 95% confidence interval obtained by marginalising/standardising of the risk ratio model[2] (Table 2). Should the risk ratio model fail to converge, GEE with Poisson outcomes, a logarithmic link, exchangeable working correlation and robust standard errors will be employed[3].

Analysis of Secondary and Tertiary Outcomes

Analysis of clinically significant upper GI bleeding, *C. difficile* infection, and ventilator associated conditions will follow the same approach as for the primary outcome, reporting risk ratios and 95% confidence intervals.

Time to discharge alive from index ICU and index hospital admission, and liberation from invasive mechanical ventilation will be summarised with medians and interquartile ranges obtained from cumulative incidence functions regarding mortality as a competing risk[4]. Treatment group comparisons will use Cox regression with covariate adjustment for the order of administration of treatments, and the batch-by-order interaction, with stratification by ICU, and robust standard errors clustered at ICU level (for any residual within-ICU correlation) to estimate cause-specific hazard ratios and confidence intervals, with patients dying prior to discharge (or extubation) censored at their time of death[4]. Assessment of the proportionality of hazards assumption in these models will be made using Schoenfeld residuals, with resultant covariate stratification or modelling of time-dependent treatment effects, where necessary. For the duration of invasive mechanical ventilation outcome, if the recorded duration of mechanical ventilation for a patient is within 48 hours of their duration of hospital stay resulting in death, then it will be assumed that such patients were extubated at that time with palliative intent and, hence, these patients' data will be censored at their time of extubation in the analyses.

Sensitivity analyses

Sensitivity to missing data in the primary and secondary outcomes

The main sensitivity analyses for the impact of missing primary and secondary outcomes will involve imputing outcomes under "worst-best" and "best-worst" case scenarios[5]. In the "worst-best" scenario for a binary outcome, a "worst" outcome event (e.g. in-hospital death within 90 days) is assigned to all patients missing the outcome in one treatment group, and a "best" outcome event (e.g. survival to hospital discharge within 90 days) is assigned to all patients missing the outcome in the other treatment group. The "best-worst" scenario is the exact opposite assignment of outcomes. For duration outcomes, the imputed values will be 0.001 days for the "best" case and a number larger than the maximum observed value for the "worst" case. Data with the best-worst and worst-best imputed outcomes will be analysed and the difference in the resulting two estimated treatment effects will indicate the range of uncertainty due to missing data for each outcome. If substantively different conclusions do not arise from these two analyses then no further missing data assessments will be performed for that outcome. If a substantively different conclusion does arise, then a more refined sensitivity analysis will employ a complete case log-binomial GEE (for binary) or Cox (for time-to-event) regression analysis adjusting for baseline covariates predictive of missingness of the specific outcome. These analyses use data from all patients who have complete outcome data, and are valid under the "covariate missing at random assumption" that missingness depends on the baseline covariates only and not on the value of the missing outcome itself or of other outcomes[6]. If more than 5% of the data for a primary or secondary outcome are missing[5], and when one outcome is missing for a patient but other outcomes are present, further sensitivity analyses will use multiple imputation methods using an imputation method that takes into account the outcomes that are available and the clustered data structure.

Additional analyses

Additional sensitivity analyses will (i) adjust for patient-level variables that exhibit imbalance across treatment groups within sequences, and (ii) exclude all patients transferred in from another ICU to the study ICU for the index admission.

Subgroup analyses

Planned subgroup analyses will assess heterogeneity of treatment effects for the primary and secondary outcomes across the following factors: (i) admitted to the ICU after cardiac surgery versus any other reason; (ii) emergency versus elective admissions, and (iii) region (sites from Ireland will be combined with UK sites and sites from Australia will be combined with New Zealand sites). These analyses will include interaction terms between treatment and subgroup in each of the respective regression models.

PROPOSED TABLES

Table 1: Baseline characteristics

ICU Characteristics	Sequence PPI/H2RB (number of ICUs=xxx)		Sequence H2RB/PPI (number of ICUs=xxx)	
Region – n (%)				
ANZ	x (x)		x (x)	
Canada	x (x)		x (x)	
Ireland	x (x)		x (x)	
UK	x (x)		x (x)	
Number of beds	x±x		x±x	
Number of ICU admissions	x±x		x±x	
Type of ICU – n (%)	x (x)		x (x)	
Tertiary ICU (medical & surgical)	x (x)		x (x)	
Tertiary ICU (surgical)	x (x)		x (x)	
Tertiary ICU (medical)	x (x)		x (x)	
Non-tertiary ICU	x (x)		x (x)	
Patient Characteristics	**Period 1 PPI (n=xx)**	**Period 2 H_2RB (n=xx)**	**Period 1 H_2RB (n=xx)**	**Period 2 PPI (n=xx)**
Age – yr	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Co-morbid conditions – no. (%)				
Respiratory	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hepatic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Immunosuppression	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Metastatic cancer	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Admission type – no. (%)				
Operative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Non-operative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Source of admission to ICU – no. (%)				
Emergency department	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
From OT following elective surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
From OT following emergency surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
APACHE-II score*	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx
APACHE-III score†	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]
ANZ risk of death score (ANZ participants only)	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx
ICNARC risk of death score (UK participants only)	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx

Plus-minus values will be expressed as mean ± SD
* Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.
† Scores on the APACHE III range from 0-299, with higher scores indicating more severe disease and a higher risk of death.
Abbreviations: ANZ: Australia & New Zealand; APACHE: Acute Physiology And Chronic Health Evaluation; ICNARC: Intensive Care National Audit & Research Centre; ICU: Intensive Care Unit; OT: operating theatre.

Table 2: Outcomes

	Default* PPI strategy (n=xxx)	Default* H_2RB strategy (n=xxx)	Estimate (95% CI)	P value
Primary outcome – no. (%)				
			Risk ratio	
In-hospital mortality	xx (xx.x)	xx (xx.x)	xx (xx to xx)	x.xx
			Risk difference	
			xx (xx to xx)	x.xx
Secondary outcomes – no. (%)				
Complications – no. (%)			**Risk ratio**	
Clinically significant upper GI bleeding	xx (xx.x)	xx (xx.x)	xx (xx to xx)	
Clostridium difficile infection	xx (xx.x)	xx (xx.x)	xx (xx to xx)	
Length of stay variables† (median, IQR)			**Hazard ratio‡**	
Days until discharged alive from ICU	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)	
Days until discharged alive from Hospital	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)	
Tertiary outcomes			**Hazard ratio‡**	
Hours until liberation alive from mechanical ventilation† -median, IQR	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)	
			Risk ratio	
Ventilator associated conditions – no. § (%)	xx (xx.x)	xx (xx.x)	xx (xx to xx)	

* Two approaches to stress ulcer prophylaxis in mechanically ventilated adults implemented at the level of the ICU were compared. One approach was to use PPIs as the default therapy when stress ulcer prophylaxis was prescribed and the other approach was to use H_2RBs as the default therapy when stress ulcer prophylaxis is prescribed. Clinicians decided whether or not individual patients would receive stress ulcer prophylaxis. When a clinician chose to prescribe stress ulcer prophylaxis, the default prescription of either PPI or H2RB was that allocated to the ICU for the current study treatment period. Irrespective of the treatment that was allocated to the ICU, the treating clinician could use either a PPI or an H_2RB for a particular patient at their discretion in situations where they considered that one or other treatment was preferable.

† Median and IQR reported with mortality regarded as a competing risk. Mortality rates by treatment group relevant to each variable will be reported in table footnotes.

‡ Hazard ratio will be estimated with mortality regarded as a competing risk. Accordingly, hazard ratios here will compare the treatment arms with reference to the chance of being being discharged alive or (liberated from mechanical ventilation alive) in the next short time interval (eg day) among patients currently alive and not discharge (or currently ventilated). For example, a hazard ratio of 1.10 means a 10% higher chance of being discharged alive (or liberated alive from mechanical ventilation) in the next day in one group than the other.

§ For participants from the eight Canadian ICUs.

Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; IQR: interquartile range; PPI: proton pump inhibitor

PROPOSED SUPPLEMENTAL TABLES

Table S1: Intensive Care Admission Diagnoses – ANZ, Irish, and Canadian ICUs

Diagnostic category	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)
Operative admission diagnosis – n (%)		
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Gynaecological	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)
Metabolic	xxx (xx.x)	xxx (xx.x)
Musculoskeletal / skin	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Non-operative admission diagnosis – n (%)		
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Gynaecological	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)
Metabolic	xxx (xx.x)	xxx (xx.x)
Musculoskeletal / skin		
Neurological	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)

Abbreviations: ANZ: Australia and New Zealand; H_2RB: histamine-2 receptor blocker; ICUs: Intensive Care Units; PPI: proton pump inhibitor.

Table S2: Intensive Care Admission Diagnoses – UK ICUs

Diagnostic category	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)
Operative admission diagnosis – n (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Poisoning	xxx (xx.x)	xxx (xx.x)
Genito-urinary	xxx (xx.x)	xxx (xx.x)
Endocrine and metabolic	xxx (xx.x)	xxx (xx.x)
Haematological/Immunological	xxx (xx.x)	xxx (xx.x)
Musculoskeletal	xxx (xx.x)	xxx (xx.x)
Dermatological	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Non-operative admission diagnosis – n (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Poisoning	xxx (xx.x)	xxx (xx.x)
Genito-urinary	xxx (xx.x)	xxx (xx.x)
Endocrine and metabolic	xxx (xx.x)	xxx (xx.x)
Haematological/Immunological	xxx (xx.x)	xxx (xx.x)
Musculoskeletal	xxx (xx.x)	xxx (xx.x)
Dermatological	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Psychiatric	xxx (xx.x)	xxx (xx.x)

Abbreviations: UK: United Kingdom; H_2RB: histamine-2 receptor blocker; ICUs: Intensive Care Units; PPI: proton pump inhibitor

Table S3. Subgroup analyses – patient factors

	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)	Estimate (95% CI)	Interaction P value
In-hospital mortality within 90 days– no. (%)				
Admitted to ICU following cardiac surgery			Risk ratio	
Yes	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
No	xx (xx.x)	xx (xx.x)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Clinically significant upper GI bleeding – no (%)				
Admitted to ICU following cardiac surgery			Risk ratio	
Yes	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
No	xx (xx.x)	xx (xx.x)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Clostridium difficile infection – no (%)				
Admitted to ICU following cardiac surgery			Risk ratio	
Yes	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
No	xx (xx.x)	xx (xx.x)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index ICU admission – median, IQR*				
Admitted to ICU following cardiac surgery			Hazard ratio†	
Yes	xx (xx-xx)	xx (xx-xx)	x (x-x)	x.xx
No	xx (xx-xx)	xx (xx-xx)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index hospital admission– median, IQR*				
Admitted to ICU following cardiac surgery			Hazard ratio†	
Yes	xx (xx-xx)	xx (xx-xx)	x (x-x)	x.xx
No	xx (xx-xx)	xx (xx-xx)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	

* Median and IQR reported with mortality regarded as a competing risk. Mortality rates by treatment group relevant to each variable will be reported in table footnotes.
† Hazard ratio will be estimated with mortality regarded as a competing risk.
Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; IQR: interquartile range; PPI: proton pump inhibitor

Table S4. Subgroup analyses – ICU-level

	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)	Estimate (95% CI)	Interaction P value
In-hospital mortality – no. (%)				
Country / Region			Risk ratio	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Clinically significant upper GI bleeding – no (%)				
Country / Region			Risk ratio	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Clostridium difficile infection – no (%)				
Country / Region			Risk ratio	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index ICU admission – median, IQR*				
Country / Region			Hazard ratio†	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index hospital – median, IQR*				
Country / Region			Hazard ratio†	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	

* Median and IQR reported with mortality regarded as a competing risk. Mortality rates by treatment group relevant to each variable will be reported in table footnotes.
† Hazard ratio will be estimated with mortality regarded as a competing risk.
Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; IQR: interquartile range; PPI: proton pump inhibitor

Table S5. Stress ulcer prophylaxis use in ICU #1*

	Default† PPI strategy (N=XXX)	Default† H_2RB strategy (N=XXX)
Monthly audit data – SUP use among ventilated adults		
Received PPI – n/N (%)	X/X (X)	X/X (X)
Received H_2RB – n/N (%)	X/X (X)	X/X (X)
Did not receive SUP – n/N (%)	X/X (X)	X/X (X)
Prescribed SUP to ventilated adults in each treatment period (mg)		
Ranitidine (enteral)	X	X
Ranitidine (intravenous)	X	X
Esomeprazole (all routes)	X	X
Omeprazole (all routes)	X	X
Pantoprazole (all routes)	X	X
SUP dispensed from the pharmacy in each treatment period (mg)		
Ranitidine (enteral)	X	X
Ranitidine (intravenous)	X	X
Esomeprazole (all routes)	X	X
Omeprazole (all routes)	X	X
Pantoprazole (all routes)	X	X

Abbreviations: IV: intravenous; SUP: stress ulcer

* An equivalent table will be presented with stress ulcer prophylaxis data for each study ICU

† Two approaches to stress ulcer prophylaxis in mechanically ventilated adults implemented at the level of the ICU were compared. One approach was to use PPIs as the default therapy when stress ulcer prophylaxis was prescribed and the other approach was to use H_2RBs as the default therapy when stress ulcer prophylaxis is prescribed. Clinicians decided whether or not individual patients would receive stress ulcer prophylaxis. When a clinician chose to prescribe stress ulcer prophylaxis, the default prescription of either PPI or H2RB was that allocated to the ICU for the current study treatment period. Irrespective of the treatment that was allocated to the ICU, the treating clinician could use either a PPI or an H_2RB for a particular patient at their discretion in situations where they considered that one or other treatment was preferable.

Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; PPI: proton pump inhibitor

PROPOSED FIGURES:

Figure 1: Participant flow diagram

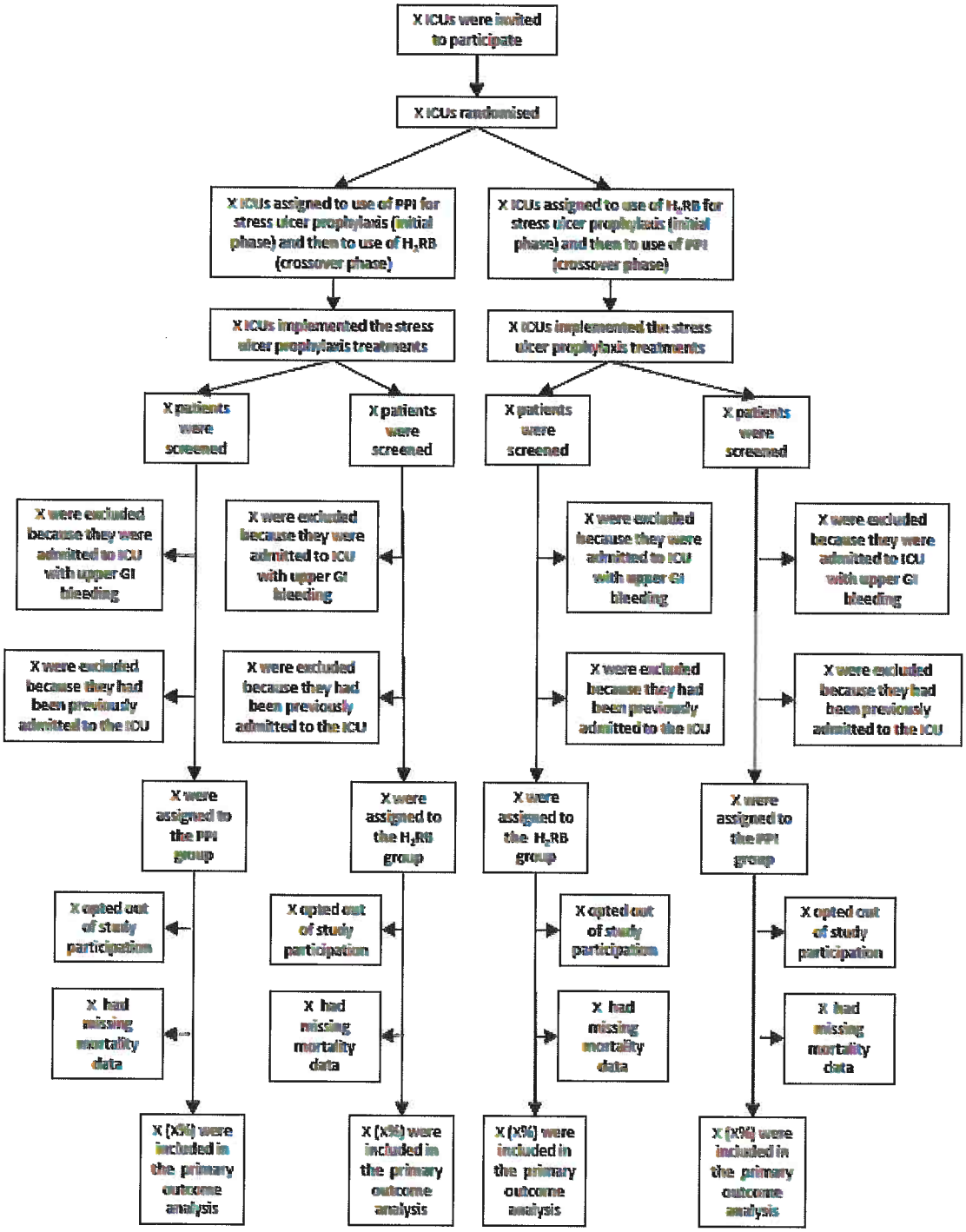

Figure 2: Estimated exposure to study treatment by sequence and treatment period

An example of the proposed lay-out is shown below with mock data for two ICUs:

Sequence PPI/H_2RB (number of ICUs=XX)			Sequence H_2RB/PPI (number of ICUs=XX)		
ICU	Period 1 PPI (n=XXXX)	Period 2 H_2RB (n=XXXX)	ICU	Period 1 H_2RB (n=XXXX)	Period 2 PPI (n=XXXX)
1			2		

Additional lines will be added for each of the study ICUs. Each Silhouette will represent 25 patients. The proportion of mechanically ventilated adults who received PPI (red), H2RB (blue), both PPI and H2RB (purple), and neither (grey) will be based on monthly audits that were performed during the conduct of the study at each site. These proportions will be multiplied by the number of patients admitted to each site in each period, divided by 25, and rounded to the nearest whole number to calculate the number of silhouettes that will be displayed. If there are fewer than 25 patients, no silhouette will be displayed.

REFERENCES:

1. Begg M, Parides M. Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *Statistics in Medicine,* 2003, 22(16), 2591-602.
2. Localio A, Margolis D, Berlin J. Relative risks and confidence intervals were easily computed indirectly from multivariable logistic regression. *Journal of Clinical Epidemiology*, 2007, 60, 874-882.
3. Yelland L, Salter A, Ryan P. Performance of the Modified Poisson Regression Approach for Estimating Relative Risks From Clustered Prospective Data. *American Journal of Epidemiology*, 2011, 174 (8), 984-992.
4. Austin P, Lee D, Fine J. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation.* 2016;133(6):601-9.
5. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Medical Research Methodology. 2017;17(1):162.
6. White I, Carpenter J, Horton N. Including all individuals is not enough: Lessons for intention-to-treat analysis. *Clinical Trials.* 2012;9(4):396-407.